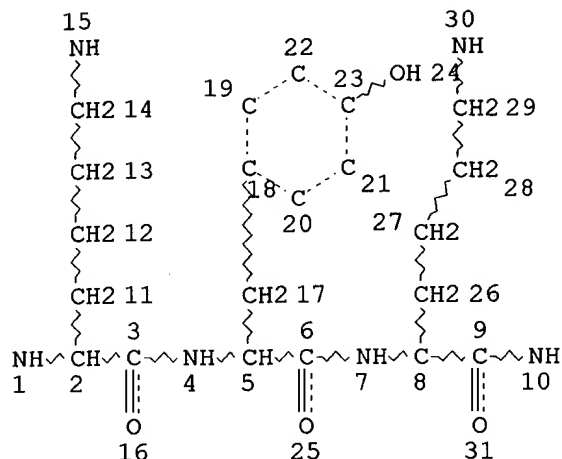


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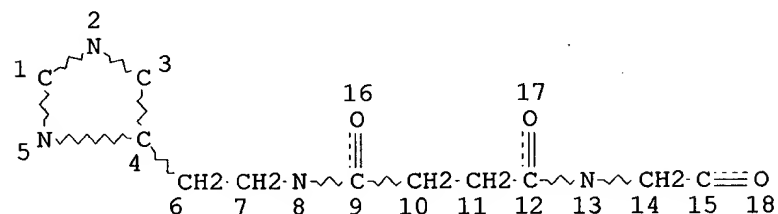
09/823,740



← core structure
(Lys-Tyr-Lys)

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STEREO ATTRIBUTES: NONE
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L15          STR
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GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 18

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L21          9 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L12 AND L17
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=> d ibib abs hitstr 121 1-9

L21 ANSWER 1 OF 9 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:51893 HCAPLUS

DOCUMENT NUMBER: 136:123598

TITLE: Production and use of novel peptide-based agents for use with bi-specific antibodies

INVENTOR(S): Hansen, Hans J.; Griffiths, Gary L.; Leung, Shui-on; McBride, William J.; Qu, Zhengxing

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 37 pp., Cont.-in-part of U. S. Ser. No. 337,756.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 14

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002006379	A1	20020117	US 2001-823746	20010403
WO 2002082041	A2	20021017	WO 2002-UST0235	20020403

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:
 US 1998-90142P P 19980622
 US 1998-104156P P 19981014
 US 1999-337756 A2 19990622
 US 2001-823746 A 20010403

AB The present invention relates to a bi-specific antibody or antibody fragment having at least one arm that is reactive against a targeted tissue and at least one other arm that is reactive against a linker moiety. The linker moiety encompasses a hapten to which antibodies have been prep'd. The antigenic linker is conjugated to one or more therapeutic or diagnostic agents or enzymes. The invention provides constructs and methods for producing the bispecific antibodies or antibody fragments, as well as methods for using them.

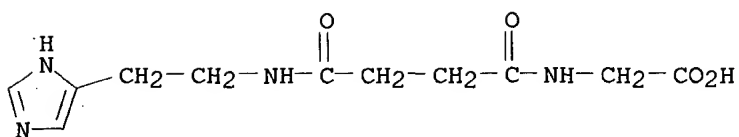
IT 192382-42-6D, Histamine succinyl glycine, conjugates
 RL: DGN (Diagnostic use); THU (Therapeutic use); BIOL (Biological study);
 USES (Uses)

(HSG; peptide-based diagnostic and therapeutic agents for use with bi-specific antibodies)

RN 192382-42-6 HCAPLUS

CN Glycine, N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]- (9CI)
 (CA INDEX NAME)

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IT **389617-27-0DP**, triazacyclononanetriacetic acid thiol-contg.
conjugates **389617-29-2DP**, triazacyclononanetriacetic acid
thiol-contg. conjugates

RL: DGN (Diagnostic use); PNU (Preparation, unclassified); THU
(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
(Uses)

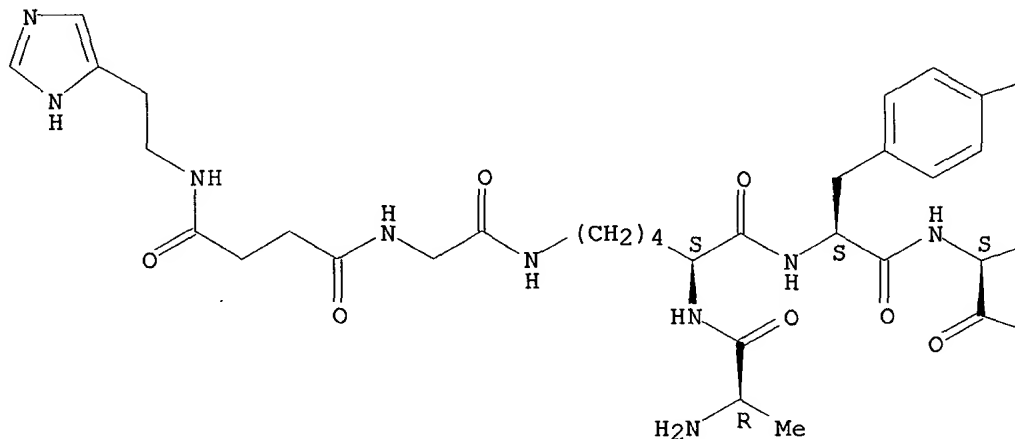
(peptide-based diagnostic and therapeutic agents for use with
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RN 389617-27-0 HCAPLUS

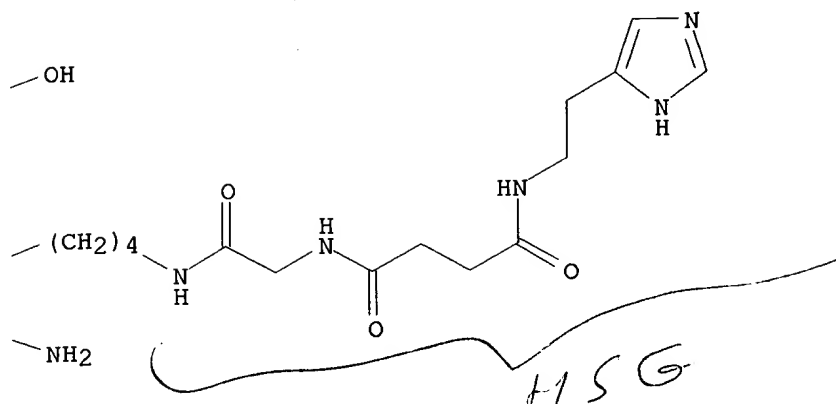
CN L-Lysinamide, D-alanyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-
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Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

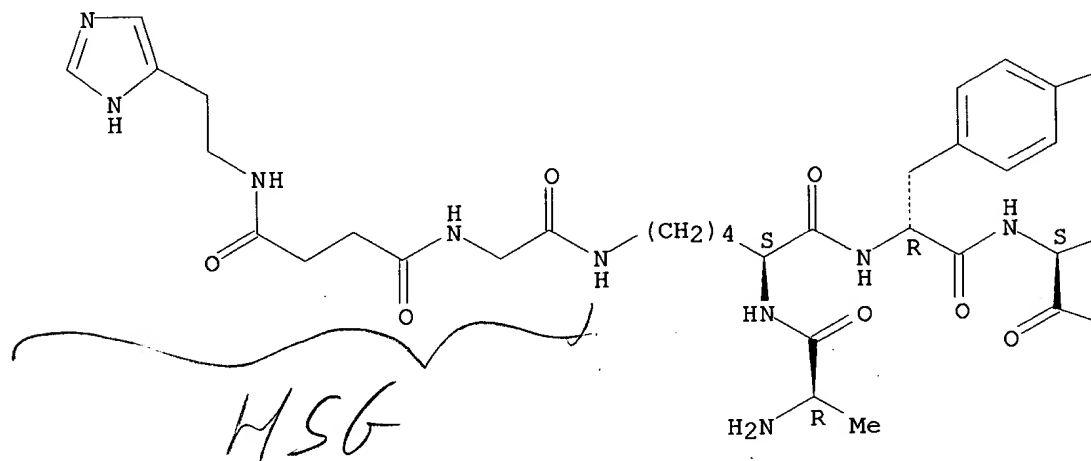


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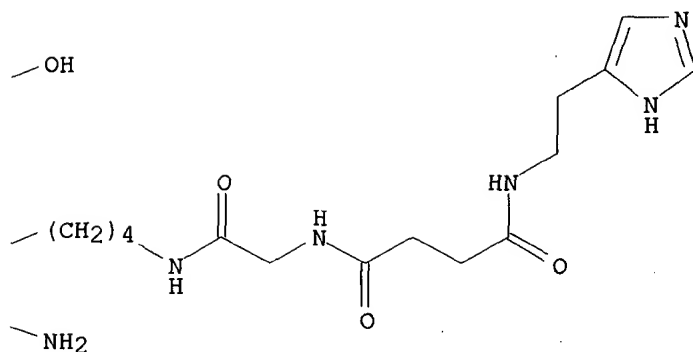
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Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



IT 391267-27-9P, IMP 241 391267-28-0P, IMP 237

391267-29-1P, IMP 243

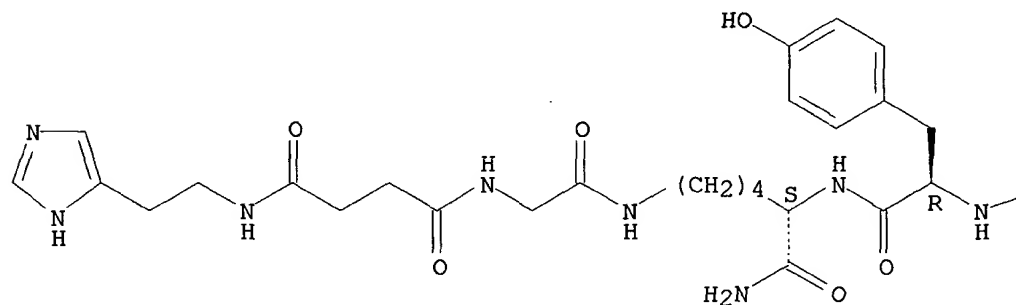
RL: DGN (Diagnostic use); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (peptide-based diagnostic and therapeutic agents for use with bi-specific antibodies)

RN 391267-27-9 HCAPLUS

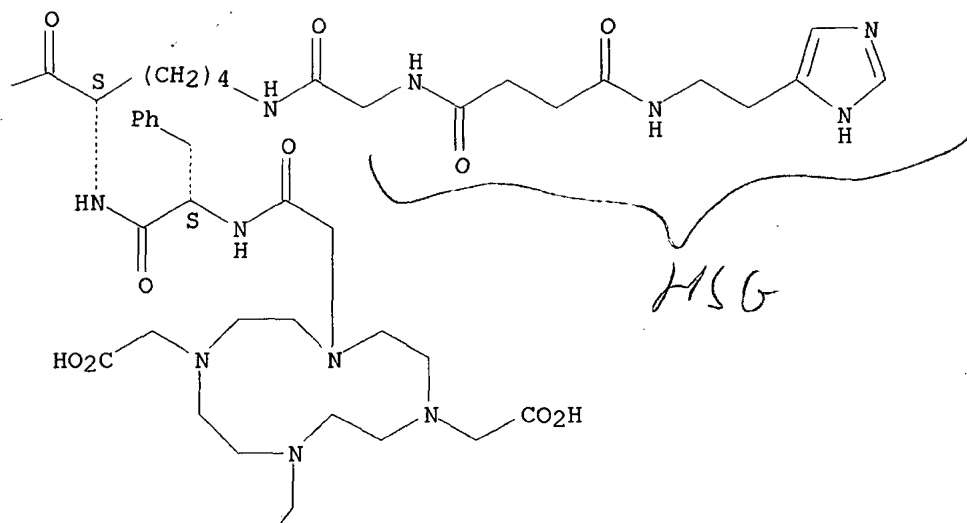
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Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



PAGE 2-B

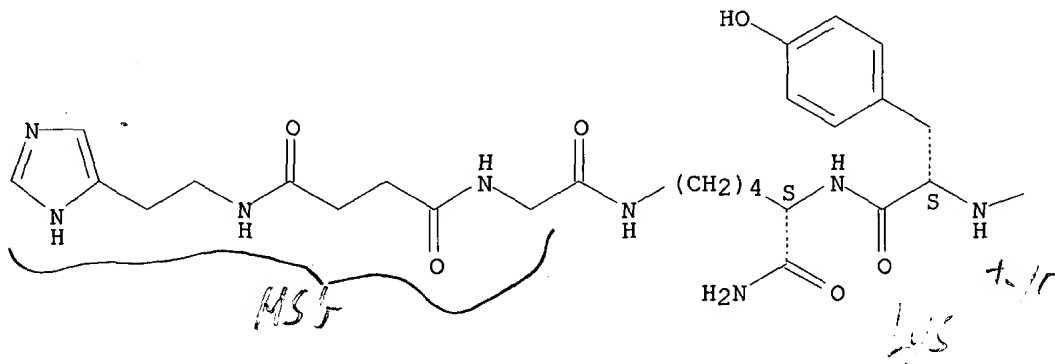
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RN 391267-28-0 HCAPLUS

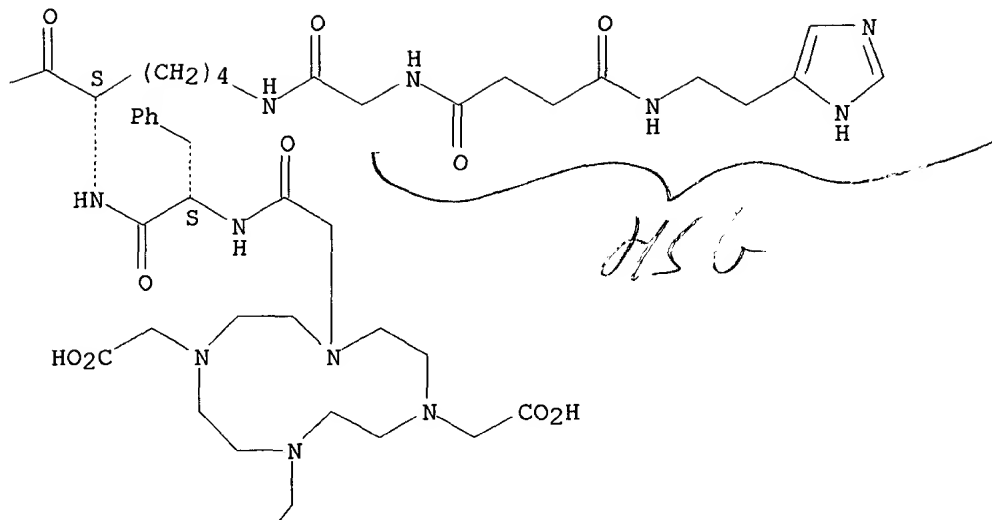
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Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



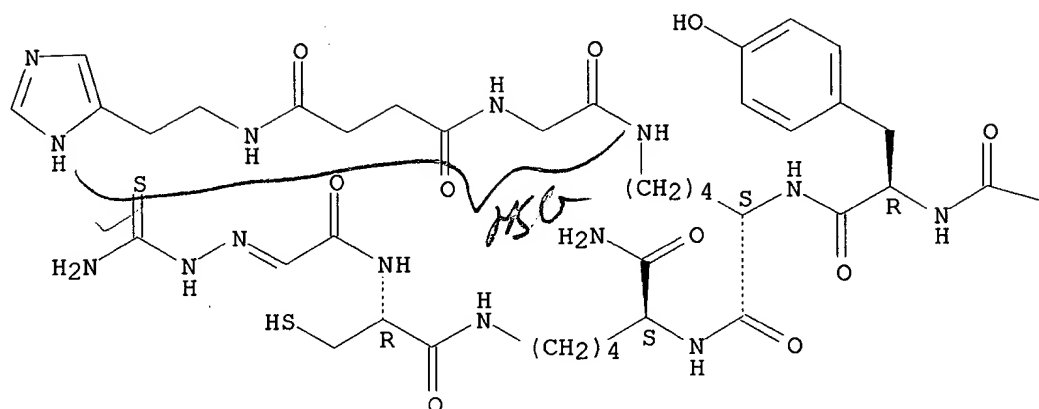
PAGE 2-B

HO₂C

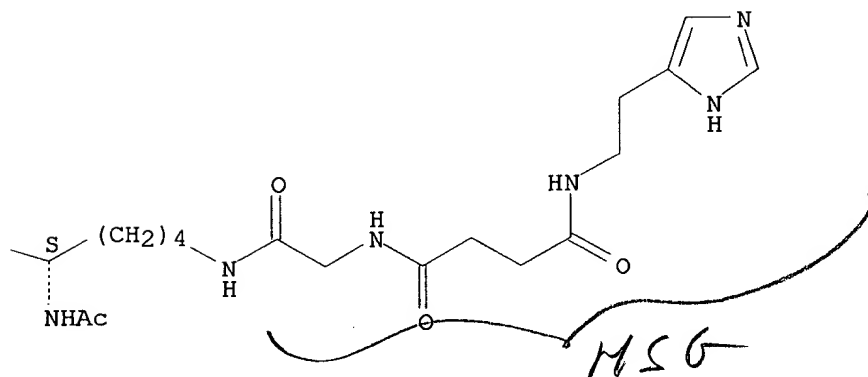
RN 391267-29-1 HCAPLUS
 CN L-Lysinamide, N2-acetyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]-L-lysyl-D-tyrosyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]-L-lysyl-N6-[N-[[(aminothioxomethyl)hydrazono]acetyl]-L-cysteiny]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry unknown.

PAGE 1-A



PAGE 1-B



> L21 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:119457 HCAPLUS

DOCUMENT NUMBER: 135:177350

TITLE: Two-step targeting of xenografted colon carcinoma using a bispecific antibody and ¹⁸⁸Re-labeled bivalent hapten: Biodistribution and dosimetry studies

AUTHOR(S): Gestin, Jean F.; Loussouarn, Anthony; Bardies, Manuel; Gautherot, Emmanuel; Gruaz-Guyon, Anne; Sai-Maurel, Catherine; Barbet, Jacques; Curtet, Chantal; Chatal, Jean F.; Faivre-Chauvet, Alain

CORPORATE SOURCE: Institut de Biologie, Institut National de la Sante et de la Recherche Medicale, Nantes, 44093, Fr.

SOURCE: Journal of Nuclear Medicine (2001), 42(1), 146-153

CODEN: JNMEAQ; ISSN: 0161-5505

PUBLISHER: Society of Nuclear Medicine, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Radioimmunotherapy (RIT) is currently being considered for the treatment of solid tumors. Although results have been encouraging for pretargeted

131I RIT with the affinity enhancement system (AES), the radionuclide used is not optimal because of its long half-life, strong .gamma. emission, poor specific activity, and low .beta. particle energy. 188Re, though unsuitable for direct antibody labeling, could be used with the AES two-step targeting technique. The purpose of this study was to compare the distribution and dosimetry of a bivalent hapten labeled with 188Re or 125I. For dosimetry calcns. and biodistribution data, 125I was substituted for 131I. After preliminary injection of a bispecific anticarcinoembryonic antigen (CEA) or antihapten antibody (Bs-mAb F6-679), AG 8.1 or AG 8.0 hapten radiolabeled with 188Re or 125I was injected into a nude mouse model grafted s.c. with a human colon carcinoma cell line (LS-174-T) expressing CEA. Not. A dosimetry study was performed for each animal from the concn. of radioactivity in tumor and different tissues. ** REG ADDED by mtd55 **. Reg. Radiolabeling of AG 8.1 with 125I afforded a 40% yield with a specific activity of 11.1 MBq/nmol after purifn. Radiolabeling of AG 8.0 with 188Re afforded a 72% yield with a specific activity of 31.82 MBq/nmol. In all expts., the percentage of tumor uptake of 125I-AG 8.1 was always significantly greater than that of 188Re-AG 8.0. The corresponding tumor-to-tissue ratios reflected uptake values. The least favorable tumor-to-normal tissue ratios in the dosimetry study were 8.1 and 8.5 for 131I (tumor-to-blood ratio and tumor-to-kidney ratio, resp.) and 2.3 for 188Re (tumor-to-intestine ratio). This study indicates that 188Re can be used for radiolabeling of hapten in two-step radioimmunotherapy protocols with the AES technique. 188Re has a greater range than 131I, which should allow the treatment of solid tumors around 1 cm in diam. Although the method used for hapten radiolabeling did not provide optimal tumor uptake, the use of a bifunctional chelating agent assocd. with AG 8.1 should solve this problem.

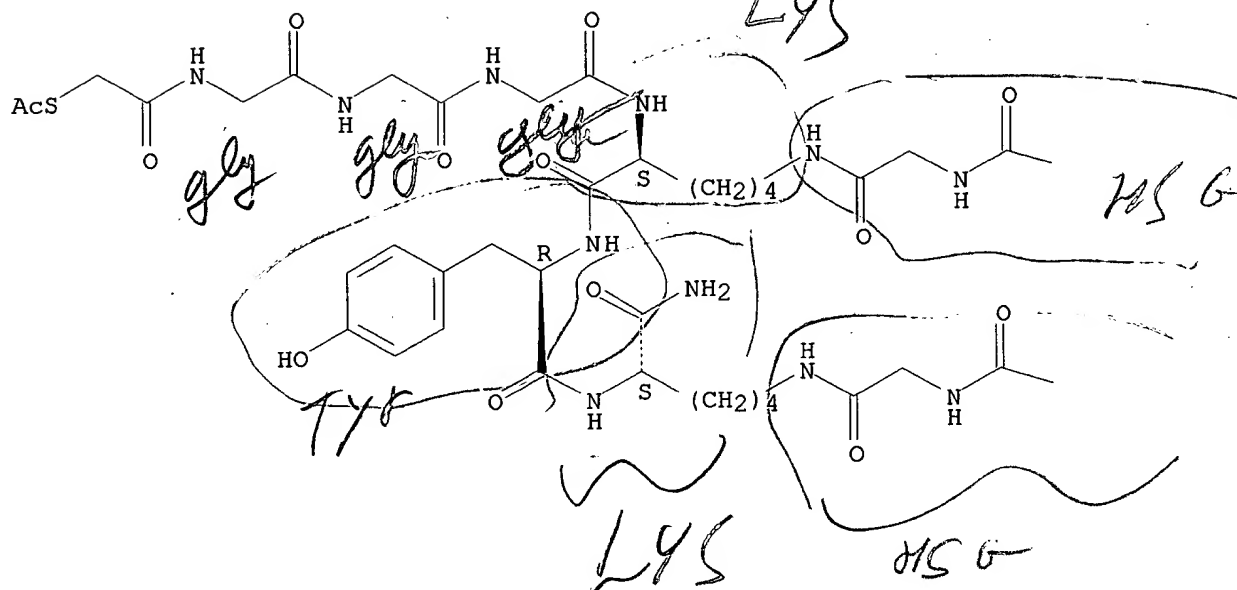
IT **159173-58-7DP**, 188Re-labeled **159173-61-2DP**, 125I-labeled
 RL: BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
 (targeting of colon carcinoma using bispecific antibody and 188Re-labeled bivalent hapten)

RN 159173-58-7 HCAPLUS

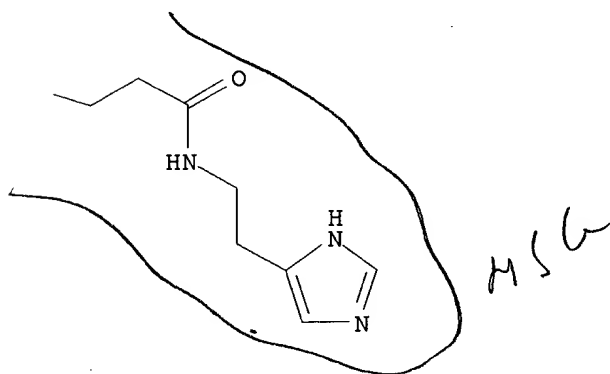
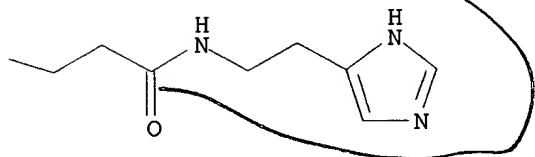
CN L-Lysinamide, N-[(acetylthio)acetyl]glycylglycylglycyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]-L-lysyl-D-tyrosyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

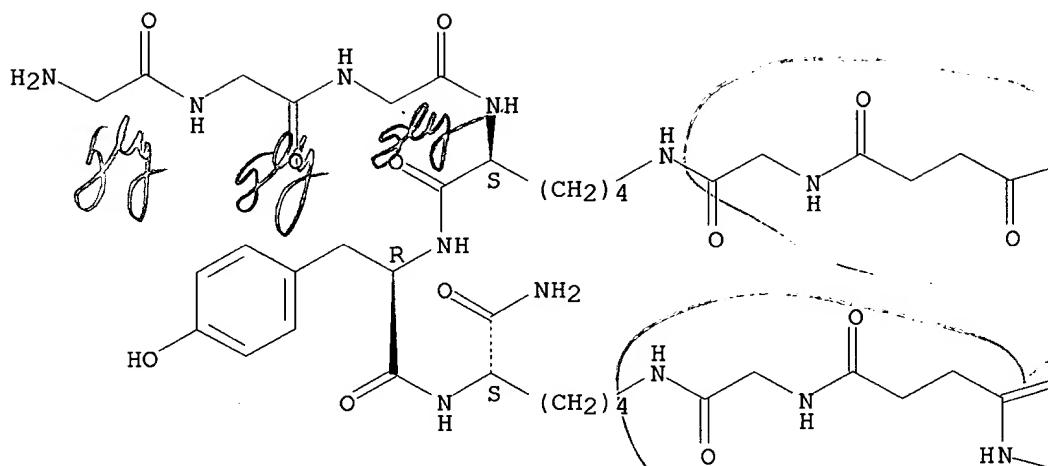


RN 159173-61-2 HCAPLUS

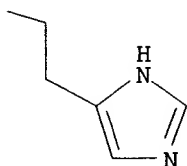
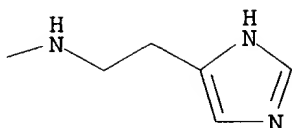
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Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT:

39

THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:479218 HCAPLUS

DOCUMENT NUMBER: 132:61055

TITLE: Two-step targeting and dosimetry for small cell lung cancer xenograft with anti-NCAM/antihistamine

AUTHOR(S): bispecific antibody and radioiodinated bivalent hapten
Hosono, Makoto; Hosono, Masako N.; Kraeber-Bodere,
Francoise; Devys, Anne; Thedrez, Philippe;
Faivre-Chauvet, Alain; Gautherot, Emmanuel; Barbet,
Jacques; Chatal, Jean-Francois
CORPORATE SOURCE: Saitama Medical Center, Saitama Medical School,
Saitama, 350-8550, Japan
SOURCE: Journal of Nuclear Medicine (1999), 40(7), 1216-1221
CODEN: JNMEAQ; ISSN: 0161-5505
PUBLISHER: Society of Nuclear Medicine, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The "affinity enhancement system," a two-step targeting technique using bispecific antibody and radiolabeled bivalent hapten, has been reported to be useful for carcinoembryonic antigen-expressing tumors. The purpose of this study was to evaluate the efficacy of this method for targeting human small cell lung cancer using an antineural cell adhesion mol. antibody. Methods: Antineural cell adhesion mol./antihistamine bispecific antibody NK1NBL1-679 was prepd. by coupling an equimol. quantity of a Fab' fragment of NK1NBL1 to a Fab fragment of antihistamine 679. Athymic mice inoculated with NCI-H69 small cell lung cancer cells expressing neural cell adhesion mol. were administered bispecific antibody and then 48 h later 125I-labeled bivalent histamine hapten. 125I-labeled intact NK1NBL1 was injected into other groups of mice. Biodistributions were examd. as a function of time. Results: In mice of the two-step targeting, tumor uptake was 2.5 \pm 0.2, 3.2 \pm 0.4, 6.4 \pm 2.0, 7.2 \pm 2.7, 6.1 \pm 2.1 and 2.2 \pm 0.4 %ID/g at 5, 30 min, 5, 24, 48 and 96 h, and tumor-to-blood, tumor-to-liver and tumor-to-kidney ratios were 1.4 \pm 1.1, 10.8 \pm 13.2 and 4.6 \pm 4.7, resp., at 5 h, whereas 125I-labeled NK1NBL1 showed a tumor uptake of 5.7 \pm 0.4 %ID/g and tumor-to-blood, tumor-to-liver and tumor-to-kidney ratios of 0.3 \pm 0.1, 1.1 \pm 0.2 and 0.9 \pm 0.1, resp., at 5 h. These results were confirmed by autoradiog. studies, which demonstrated clear tumor-to-normal tissue contrast. Dosimetry showed that the affinity enhancement system could enhance the therapeutic potential of the antineural cell adhesion mol. antibody NK1NBL1. Conclusion: This two-step targeting method seems promising for the diagnosis and therapy of small cell lung cancer.

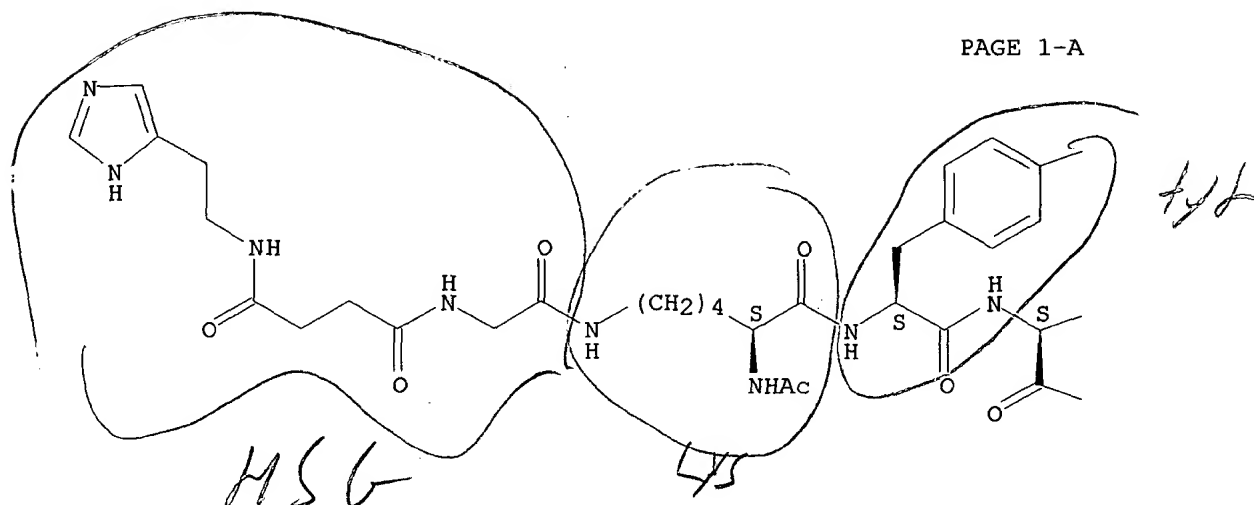
IT 136687-43-9D, 125I-labeled
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses) (two-step targeting and dosimetry for small cell lung cancer xenograft with anti-NCAM/antihistamine bispecific antibody and radioiodinated bivalent hapten)

RN 136687-43-9 HCAPLUS

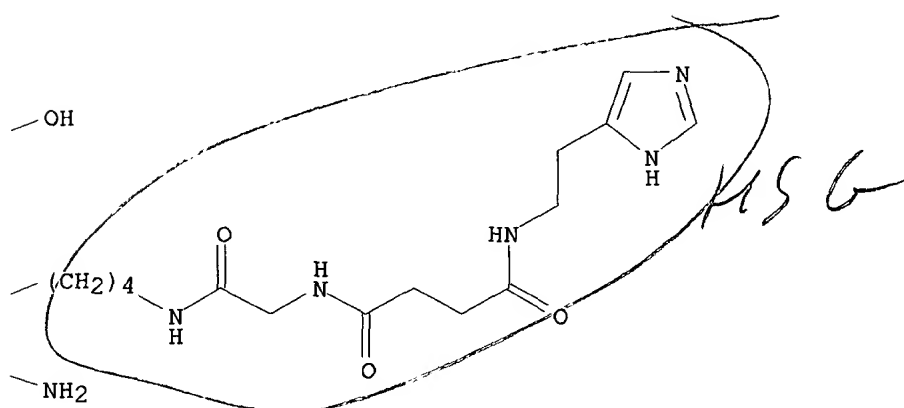
CN L-Lysinamide, N2-acetyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]-L-lysyl-L-tyrosyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:81927 HCAPLUS

DOCUMENT NUMBER: 128:215043

TITLE: Pretargeted radioimmunotherapy using ¹³¹I-labeled bivalent hapten-bearing peptides

AUTHOR(S): de Boisferon, Marc; Hillairet, Manetti, Corrine; Raguin, Olivier; Gautherot, Emmanuel; Rostene, William; Barbet, Jacques; Gruaz-Guyon, Anne
 CORPORATE SOURCE: Hopital Fac. Med. Saint Antoine, Paris, F-75012, Fr.
 SOURCE: Letters in Peptide Science (1997), 4(4/5/6), 331-339
 CODEN: LPSCEM; ISSN: 0929-5666

PUBLISHER: Kluwer Academic Publishers

DOCUMENT TYPE: Journal

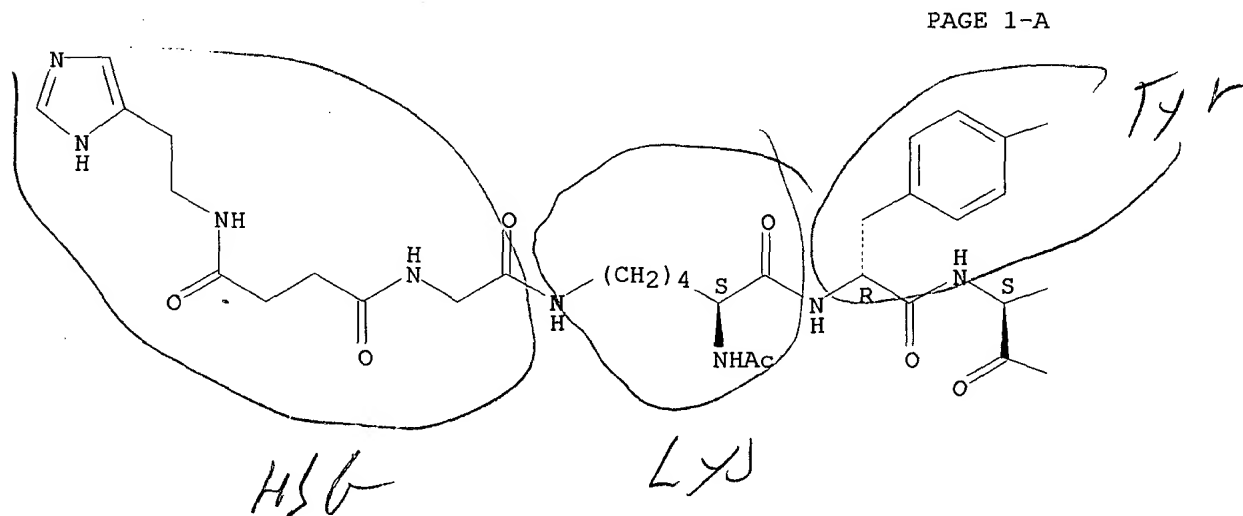
LANGUAGE: English

AB The advantages of bivalent hapten-bearing peptides for the detection of tumors pretargeted with bispecific antibodies have been demonstrated. This technol. is now considered for radioimmunotherapy and bivalent haptens designed to target ¹³¹I are needed. We thus synthesized a series of tyrosine-contg. peptides bearing the histamine-hemisuccinate hapten.

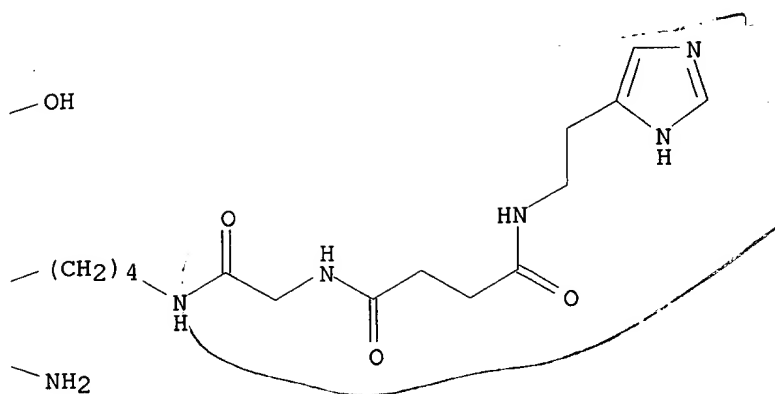
IT 173039-12-8D, 131I-labeled
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

RN 173039-12-8 HCAPLUS

Absolute stereochemistry.



PAGE 1-B



IT 173039-12-8 192370-39-1 192370-40-4
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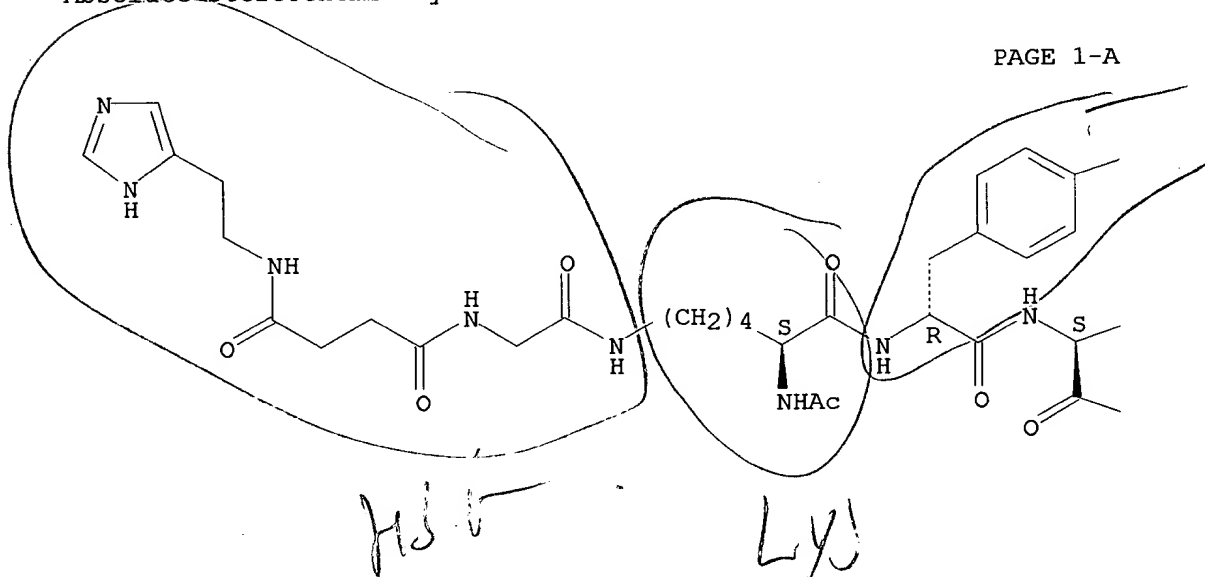
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
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 (pretargeted radioimmunotherapy using ^{131}I -labeled bivalent
 hapten-bearing peptides)

RN 173039-12-8 HCAPLUS

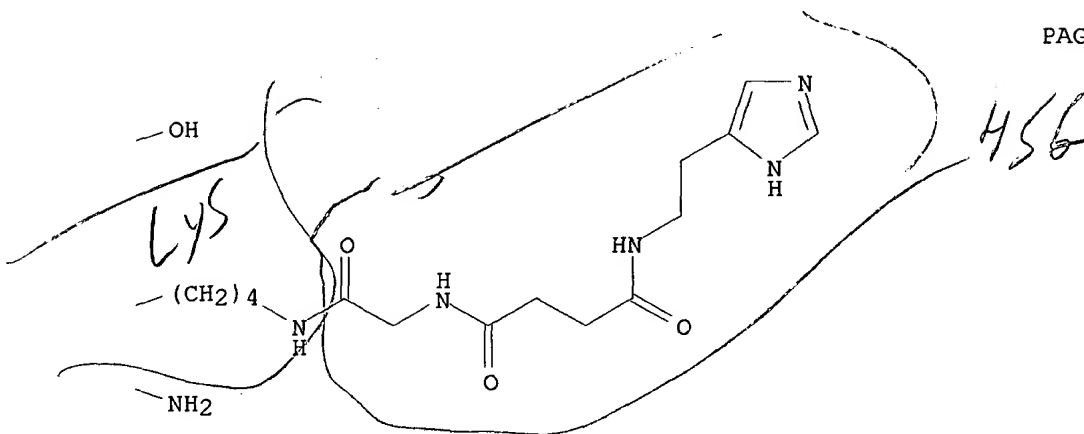
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Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

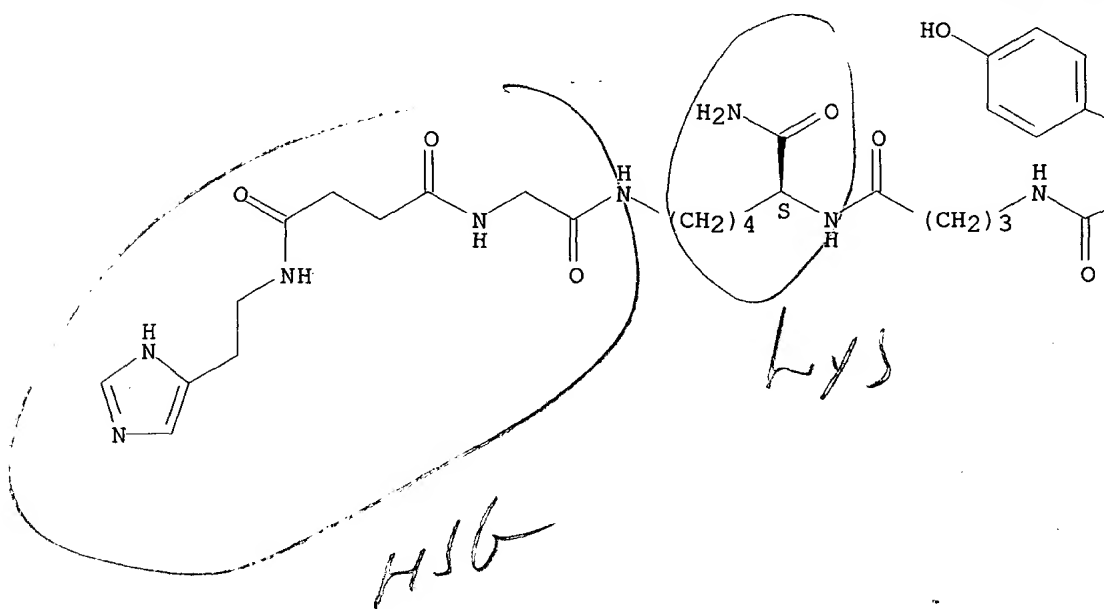


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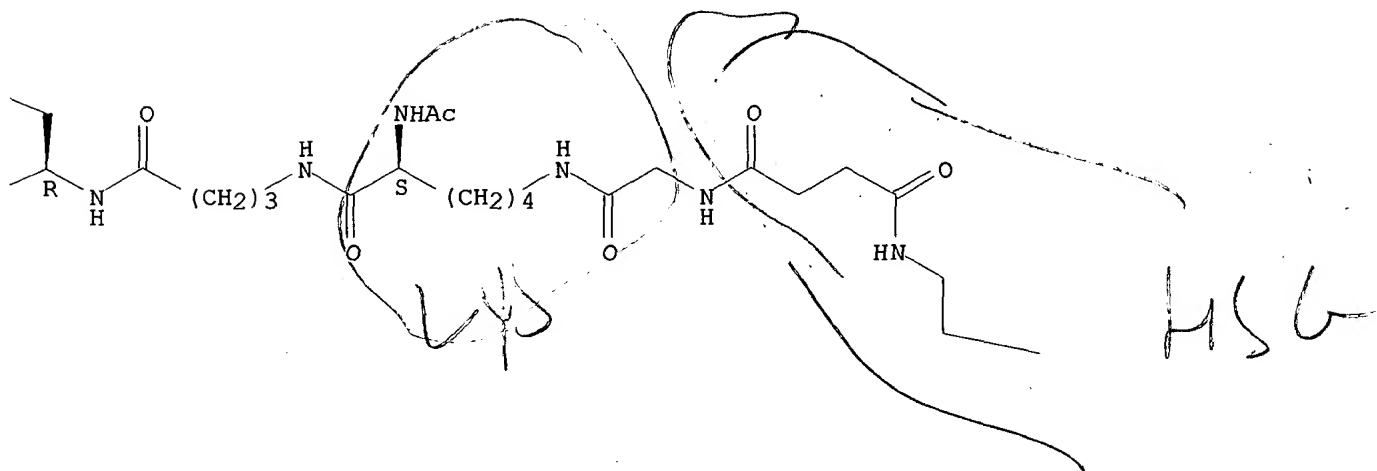
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Absolute stereochemistry.

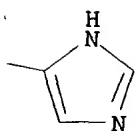
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PAGE 1-B



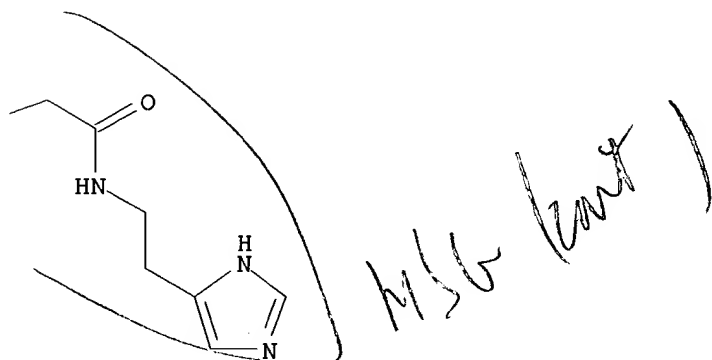
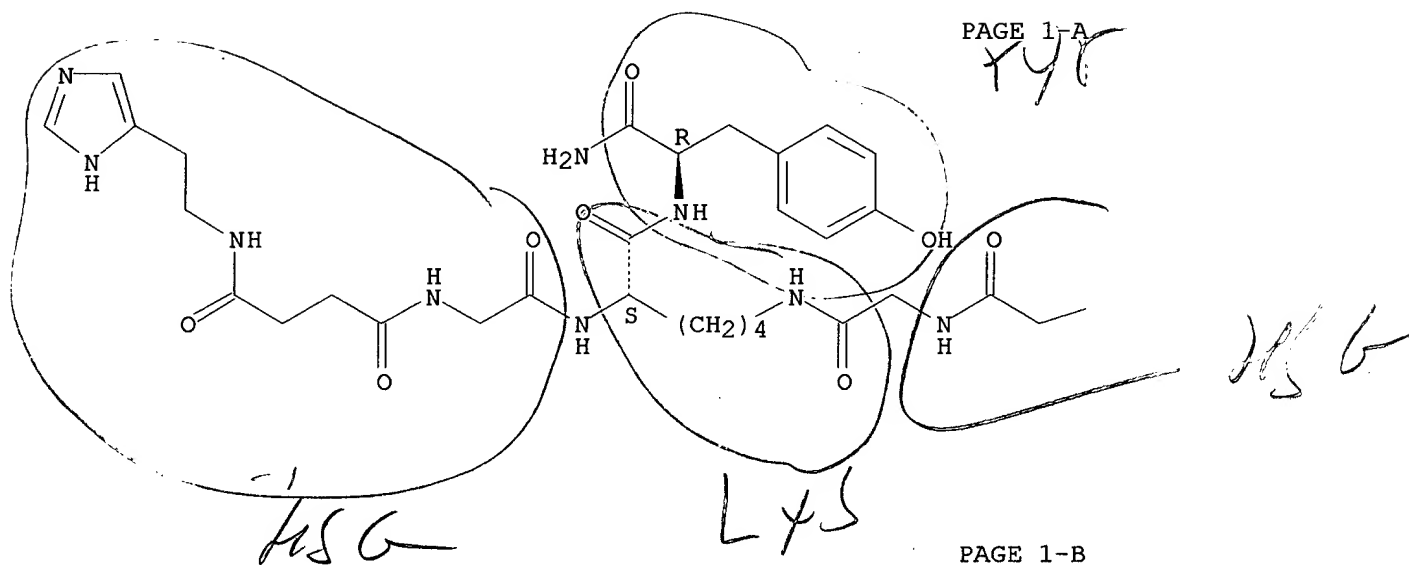
PAGE 1-C



RN 192370-40-4 HCAPLUS

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Absolute stereochemistry.

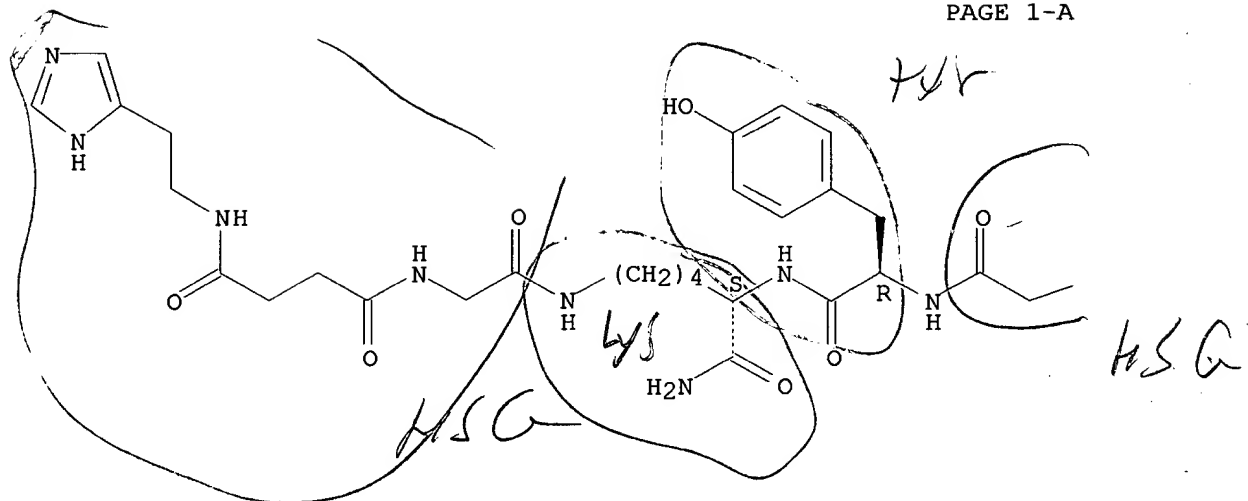


RN 192370-41-5 HCAPLUS

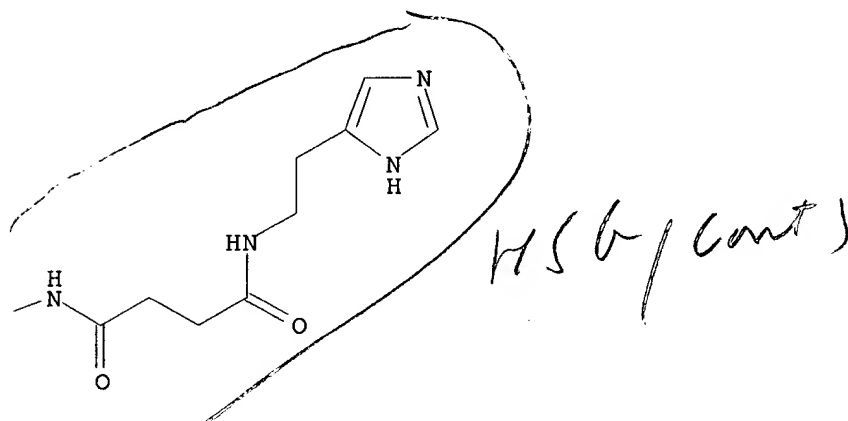
CN L-Lysinamide, N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl-D-tyrosyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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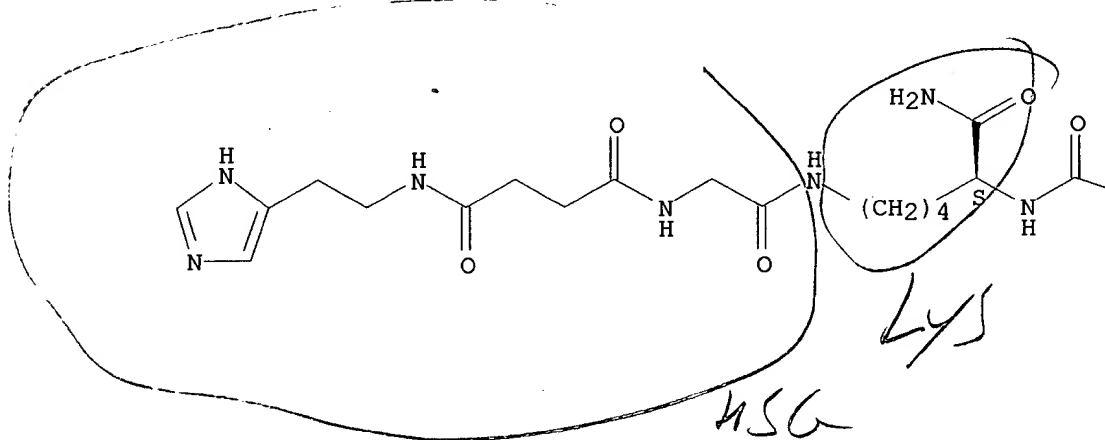


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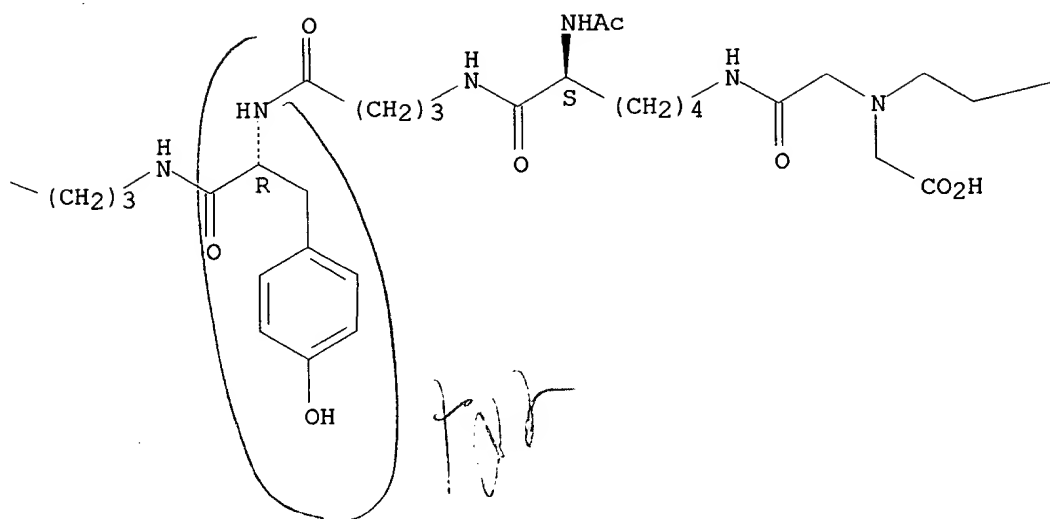
CN L-Lysinamide, N2-acetyl-N6-[N-[2-[2-[bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]ethyl]-N-(carboxymethyl)glycyl]-L-lysyl-4-aminobutanoyl-D-tyrosyl-4-aminobutanoyl-N6-[N-[4-[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

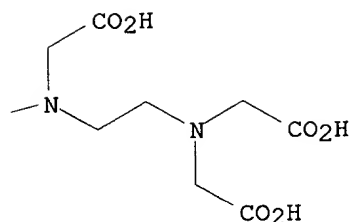
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PAGE 1-C

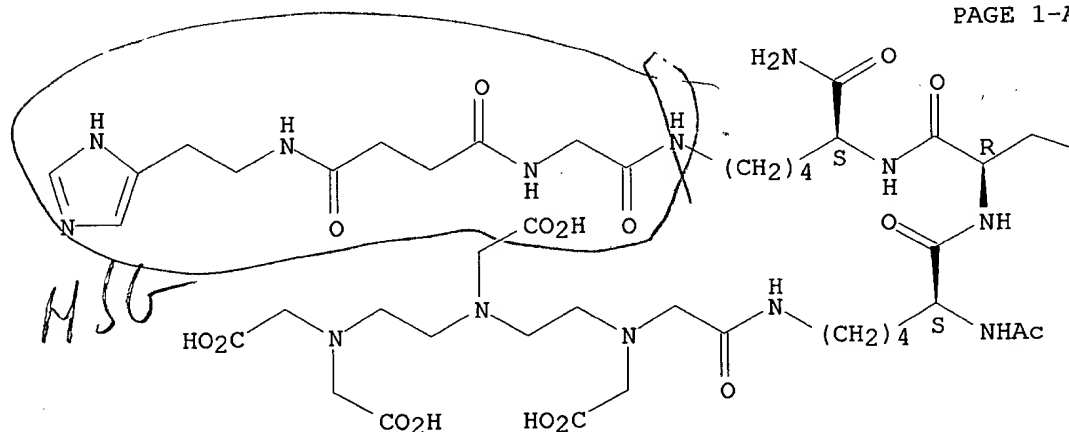


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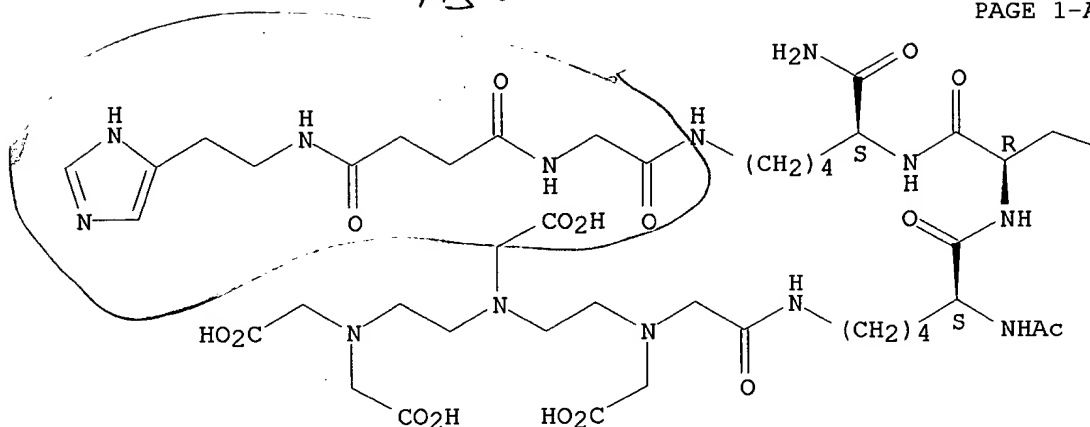
CN L-Lysinamide, N2-acetyl-N6-[N-[2-[[2-[bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]ethyl]-N-(carboxymethyl)glycyl]-L-lysyl-D-tyrosyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

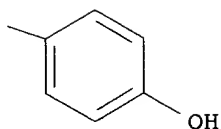
PAGE 1-A



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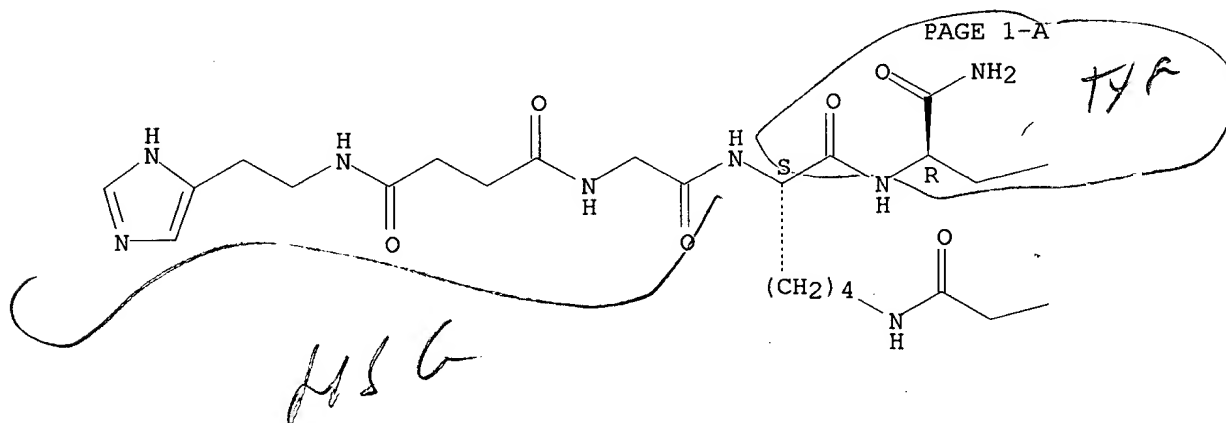
PAGE 1-B



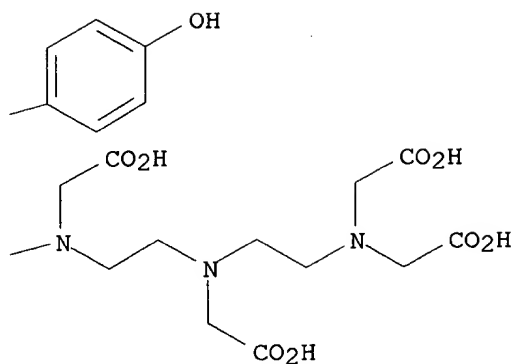
RN 192370-44-8 HCAPLUS
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Absolute stereochemistry.

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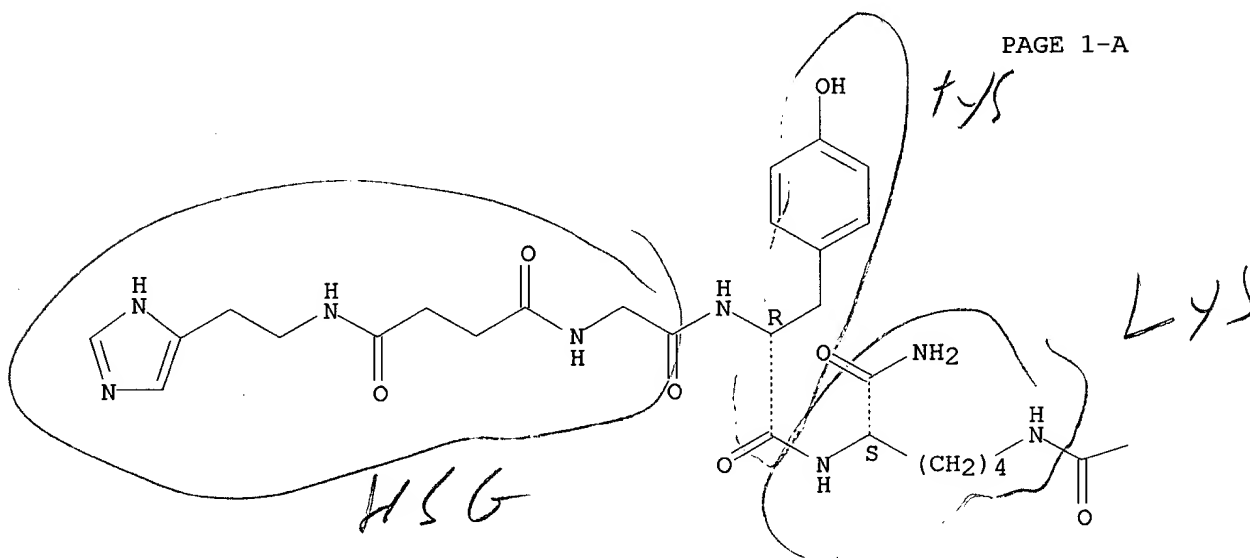


RN 192370-45-9 HCAPLUS

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Absolute stereochemistry.

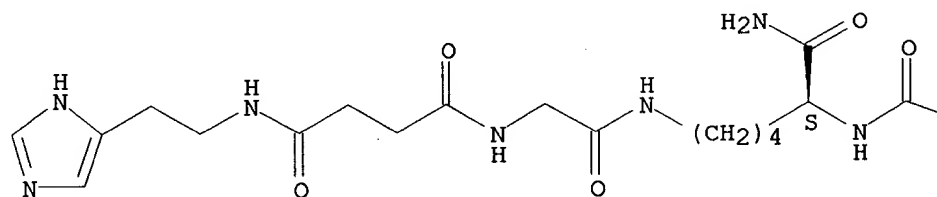
PAGE 1-A



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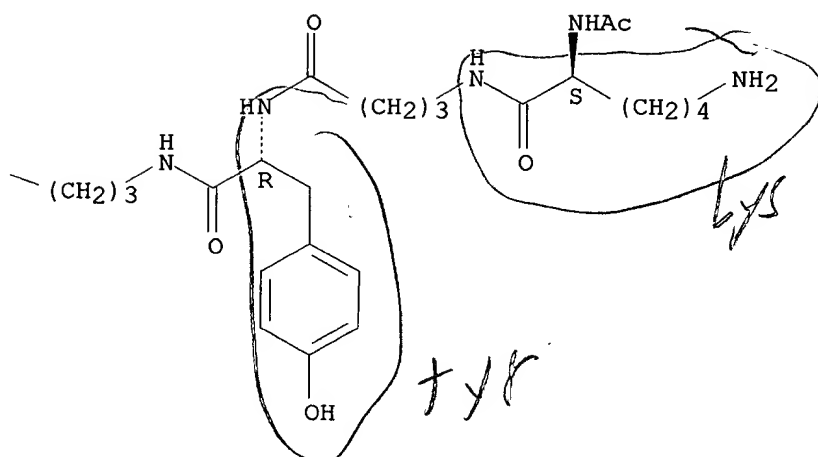
RN 192370-48-0 HCALE05
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 N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI)
 (CA INDEX NAME)

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MSG

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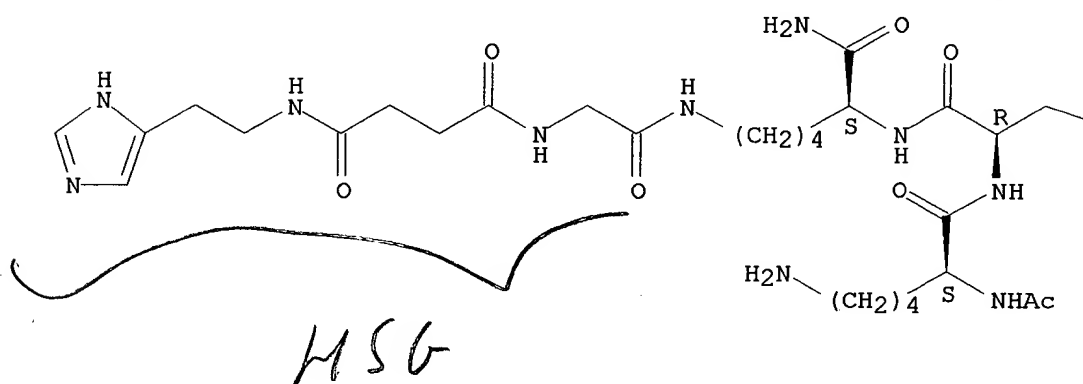


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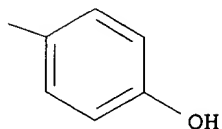
CN L-Lysinamide, N2-acetyl-L-lysyl-D-tyrosyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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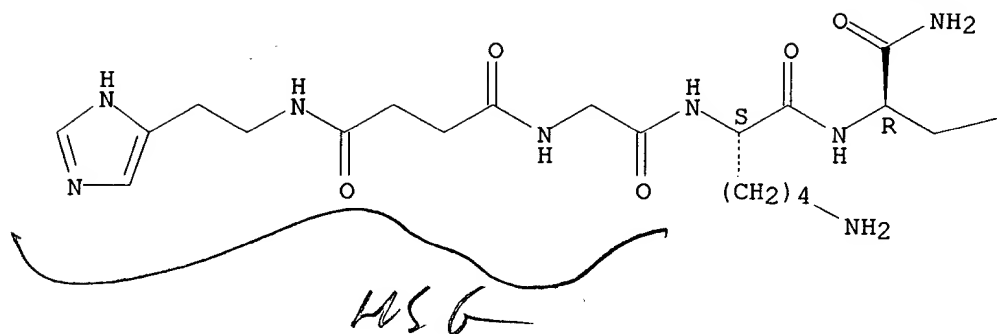


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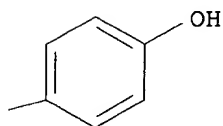
CN D-Tyrosinamide, N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl-L-lysyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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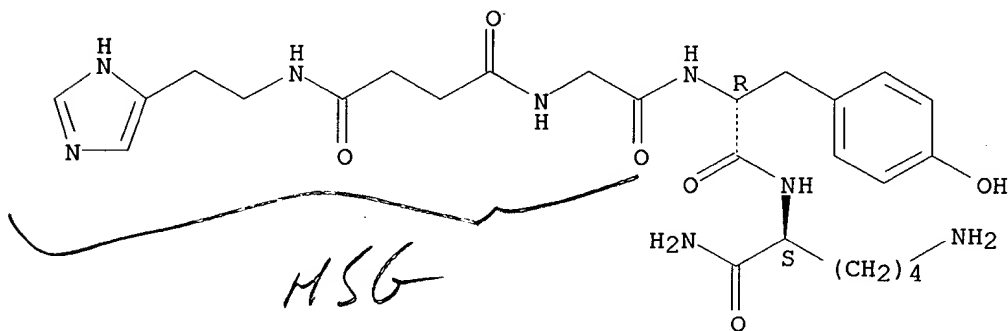
PAGE 1-B



RN 192370-49-3 HCAPLUS

CN L-Lysinamide, N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl-D-tyrosyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L21 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1997:433597 HCAPLUS

DOCUMENT NUMBER: 127:106066

TITLE: Bivalent Hapten-Bearing Peptides Designed for

Iodine-131 Pretargeted Radioimmunochemistry

AUTHOR(S): Janevik-Ivanovska, E.; Gautherot, E.; de Boisferon, M.

Hillairet; Cohen, M.; Milhaud, G.; Tartar, A.;

Rostene, W.; Barbet, J.; Gruaz-Guyon, A.

CORPORATE SOURCE: INSERM U.339 and Service de Biophysique, Faculte de

Medecine Saint Antoine, Paris, 75012, Fr.

SOURCE: Bioconjugate Chemistry (1997), 8(4), 526-533

CODEN: BCCHES; ISSN: 1043-1802

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

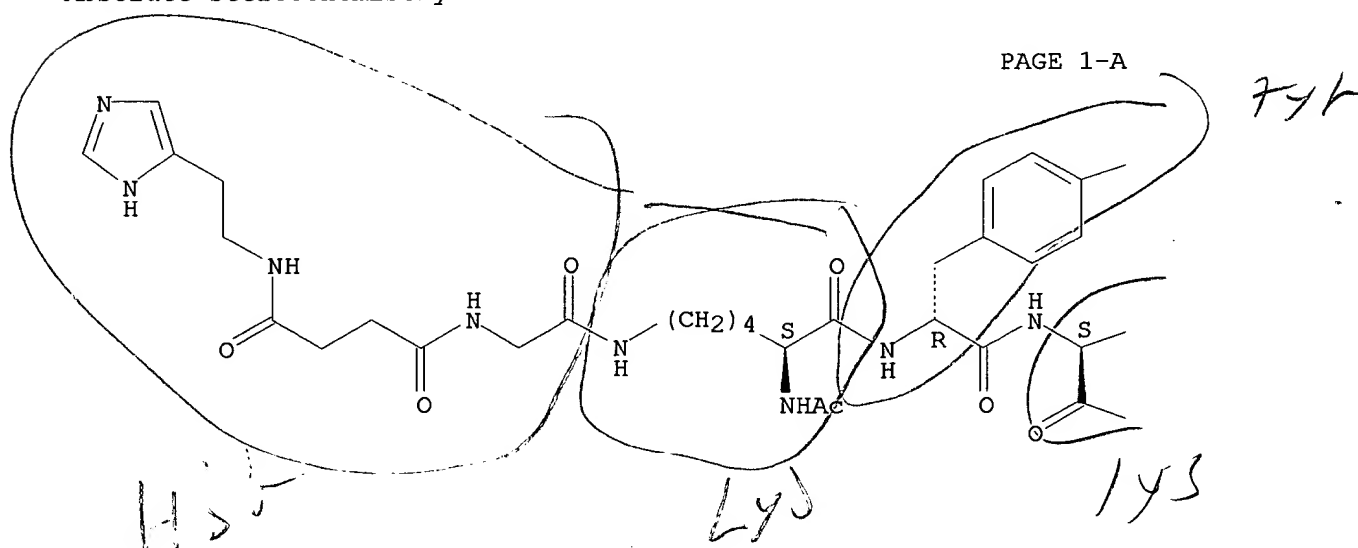
AB Pretargeting with bispecific antibodies has been used successfully for tumor detection and is now considered for radioimmunotherapy. The advantages of bivalent haptens have been demonstrated in this context. A series of bivalent mols. allowing efficient labeling with radioactive iodine has been designed for use with this new technol. They were based on the histamine-hemisuccinate hapten and prepd. by solid phase peptide synthesis. Simultaneous binding of two antibody mols. to one bivalent hapten was possible with low steric hindrance when the two hapten groups were attached to the lateral chains of lysine residues sepd. by a single amino acid. Bispecific antibodies to the hapten and to carcinoembryonic antigen were shown to mediate specific binding of the haptens to tumor cells in vitro. These expts. demonstrated that the bivalent hapten AG3.0, with a lysyl-D-tyrosyl-lysine connecting chain, possessed the best binding properties. This peptide was used to target iodine-125 to human colon cancer xenografts in nude mice. High tumor uptake and tumor to normal tissue ratios were obsd. This peptide thus appears as a good candidate for further development. Asym. bivalent haptens, with one histamine-hemisuccinate and one diethylenetriaminepentaacetic acid group, have also been prepd. and shown to be capable of binding simultaneously two specific antibody mols. These peptides should be useful to target radioiodine to cells characterized by the expression of two different antigenic markers.

IT **173039-12-8DP**, labeled with iodine-131 **192370-39-1DP**, labeled with iodine-131 **192370-40-4DP**, labeled with iodine-131 **192370-41-5DP**, labeled with iodine-131 **192370-42-6DP**, labeled with iodine-131 **192370-43-7DP**, labeled with iodine-131 **192370-44-8DP**, labeled with iodine-131 **192370-45-9DP**, labeled with iodine-131 **192370-46-0DP**, labeled with iodine-131 **192370-47-1DP**, labeled with iodine-131 **192370-48-2DP**, labeled with iodine-131 **192370-49-3DP**, labeled with iodine-131
 RL: PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (bivalent hapten-bearing peptides designed for iodine-131 pretargeted radioimmunotherapy of colon carcinoma)

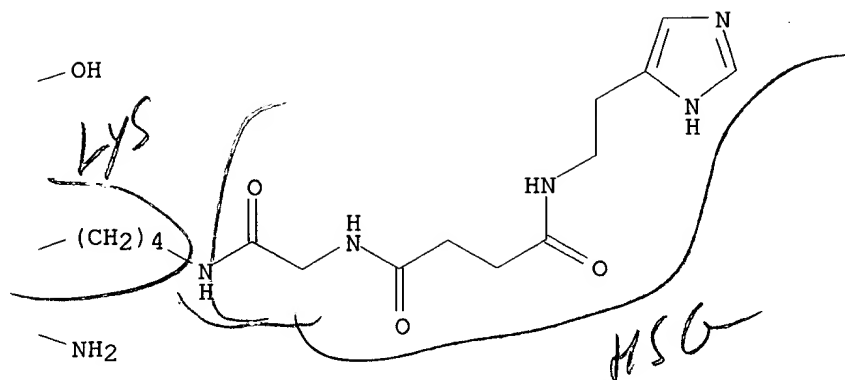
RN 173039-12-8 HCAPLUS

CN L-Lysinamide, N2-acetyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]-L-lysyl-D-tyrosyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



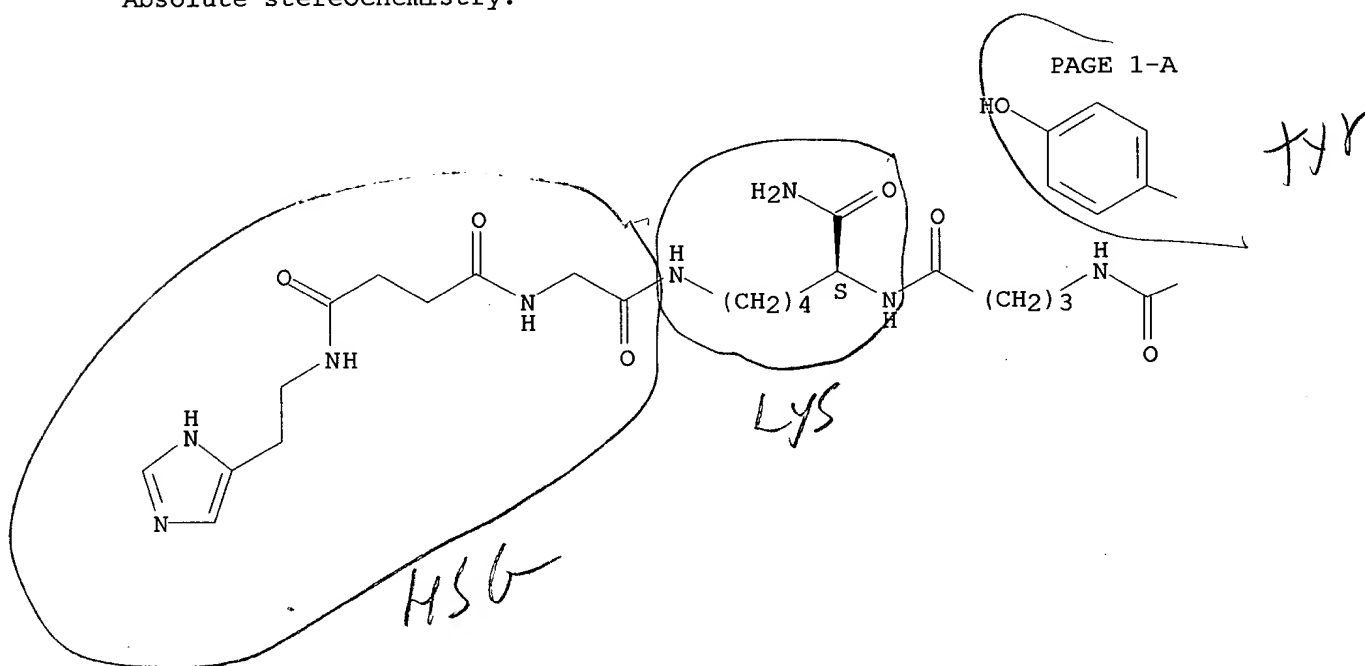
PAGE 1-B



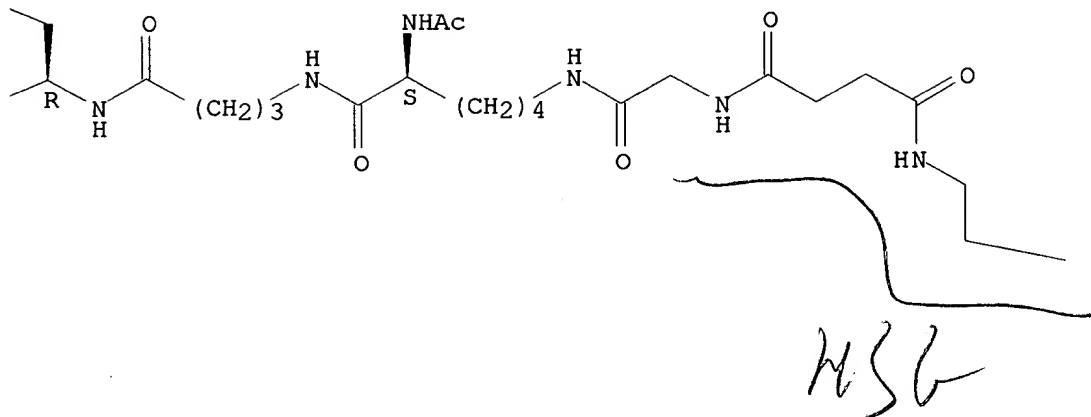
RN 192370-39-1 HCAPLUS

CN L-Lysinamide, N2-acetyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]-L-lysyl-4-aminobutanoyl-D-tyrosyl-4-aminobutanoyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

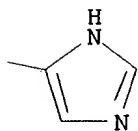
Absolute stereochemistry.



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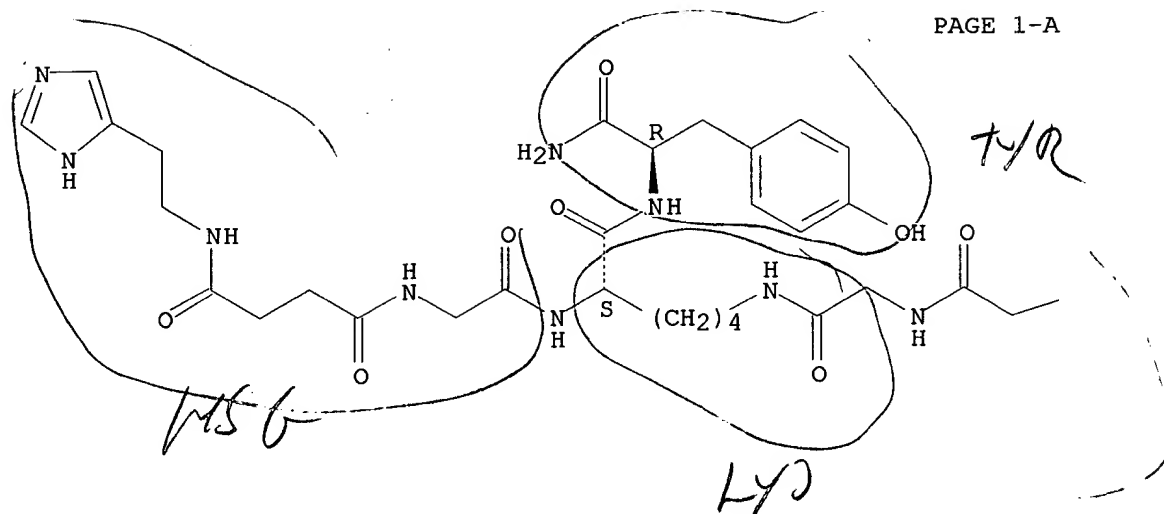


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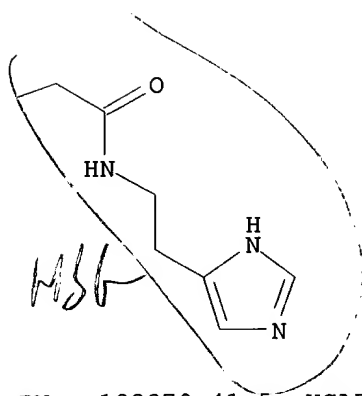
CN D-Tyrosinamide, N2,N6-bis[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]-L-lysyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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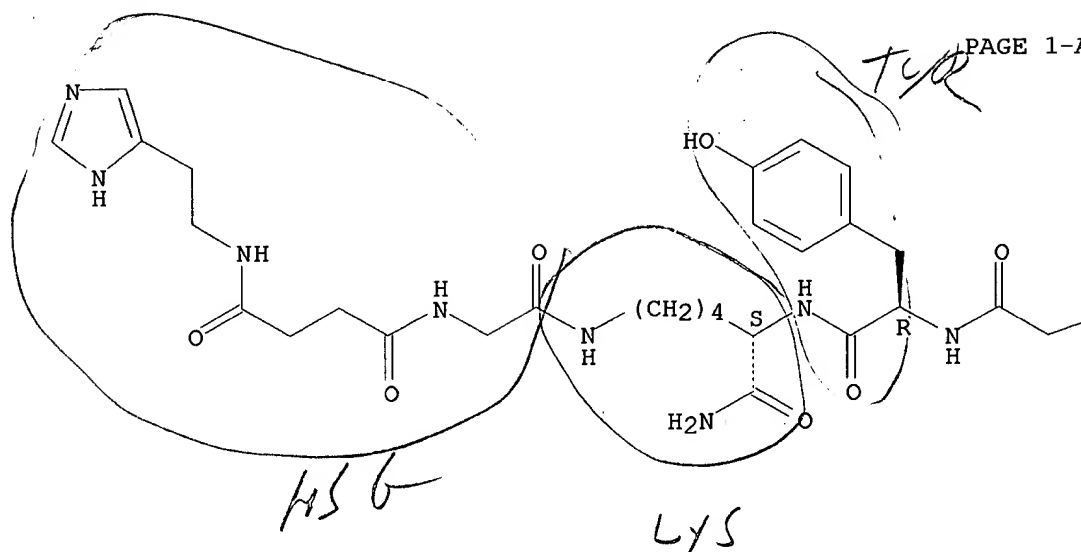


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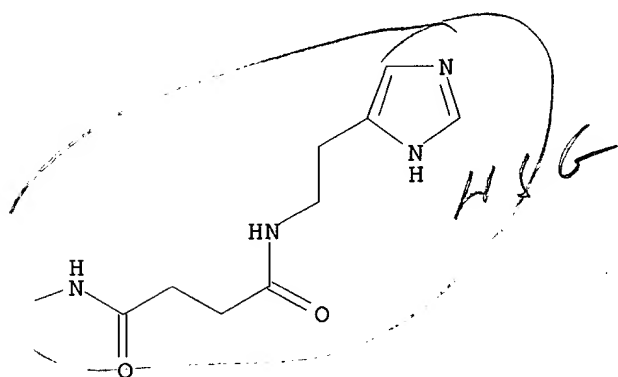
CN L-Lysinamide, N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl-D-tyrosyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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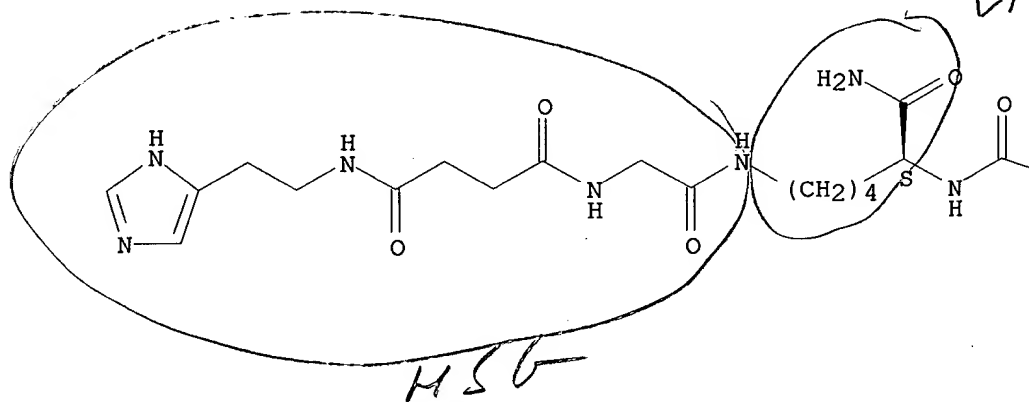


RN 192370-42-6 HCAPLUS

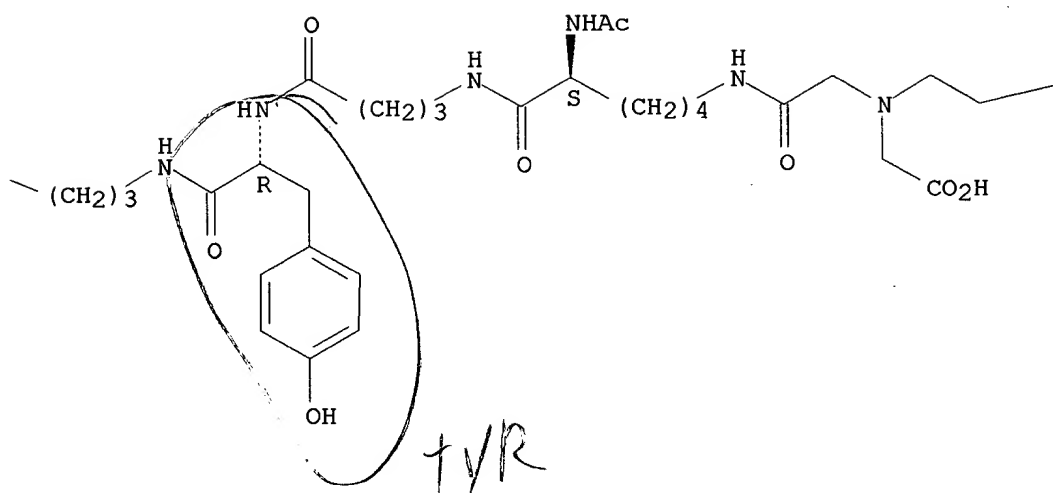
CN L-Lysinamide, N2-acetyl-N6-[N-[2-[[2-[bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]ethyl]-N-(carboxymethyl)glycyl]-L-lysyl-4-aminobutanoyl-D-tyrosyl-4-aminobutanoyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

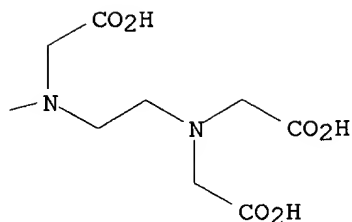
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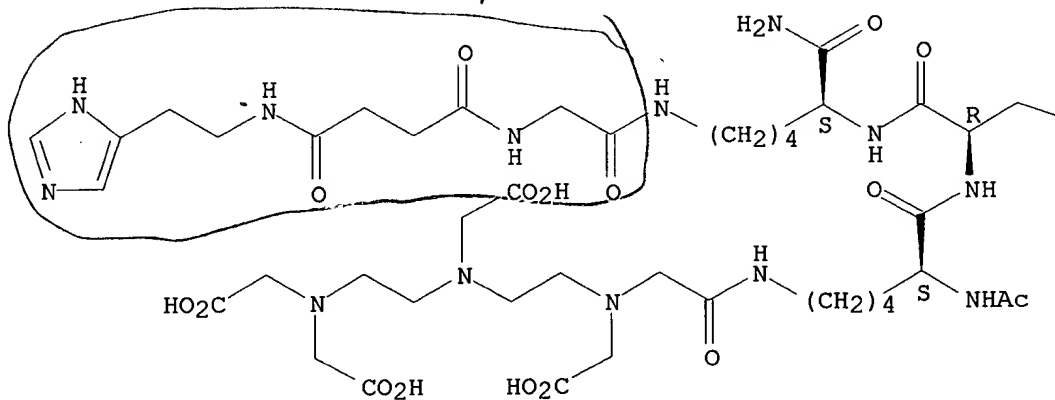


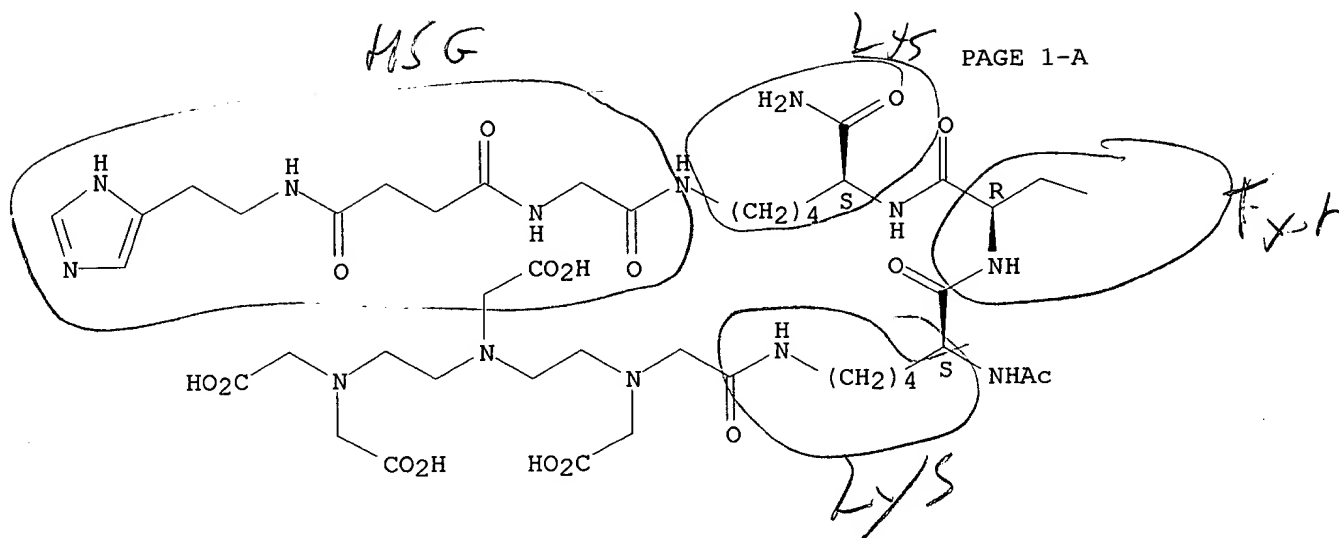
RN 192370-43-7 HCAPLUS

CN L-Lysinamide, N2-acetyl-N6-[N-[2-[[2-[bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]ethyl]-N-(carboxymethyl)glycyl]-L-lysyl-D-tyrosyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

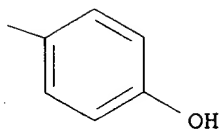
Absolute stereochemistry.

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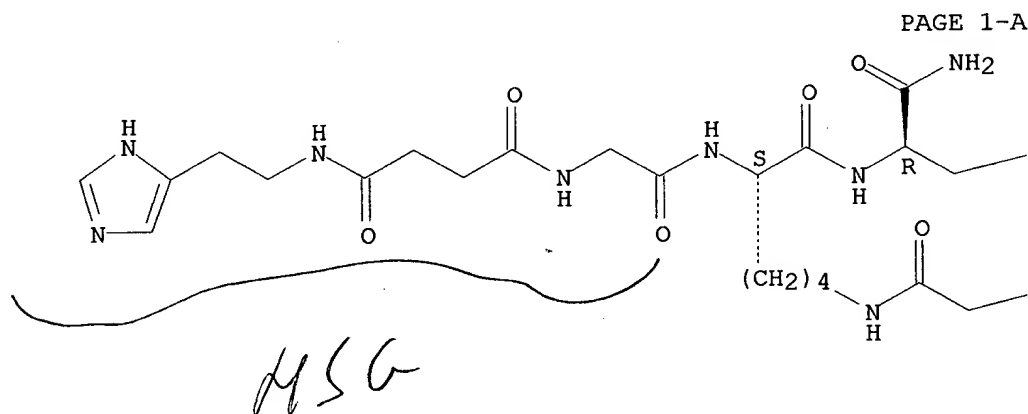
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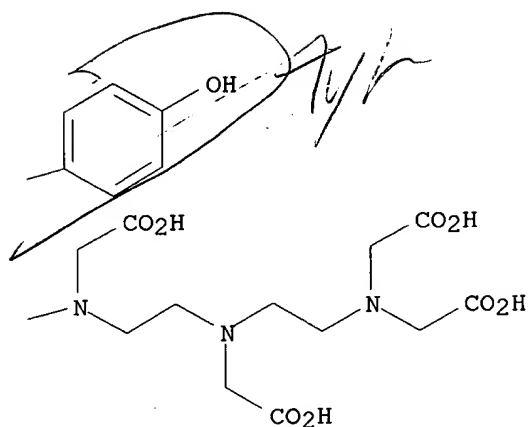
RN 192370-44-8 HCAPLUS

CN D-Tyrosinamide, N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl-N6-[N-[2-[[2-[bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]ethyl]-N-(carboxymethyl)glycyl]-L-lysyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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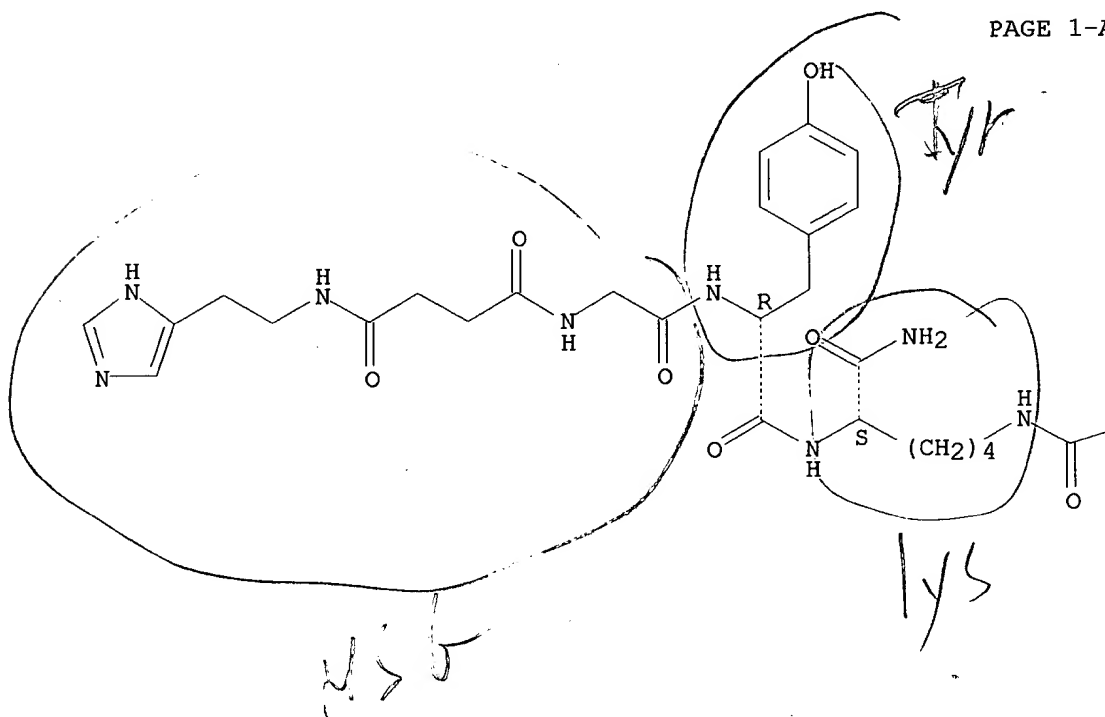


RN 192370-45-9 HCAPLUS

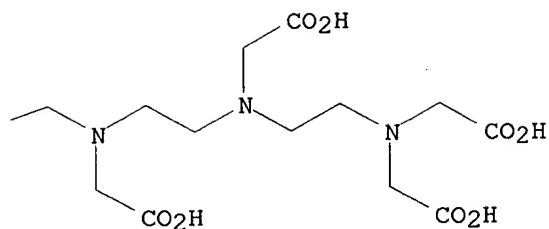
CN L-Lysinamide, N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl-D-tyrosyl-N6-[N-[2-[[2-[bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]ethyl]-N-(carboxymethyl)glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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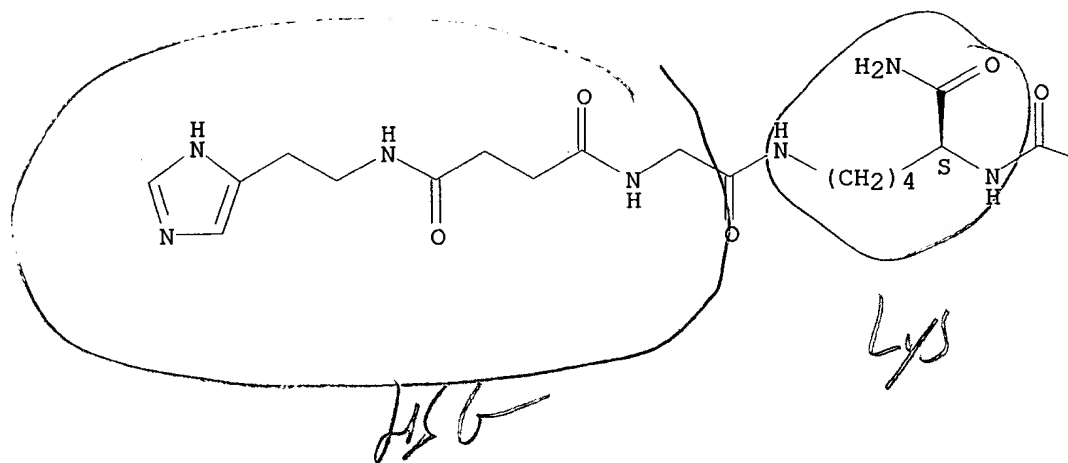


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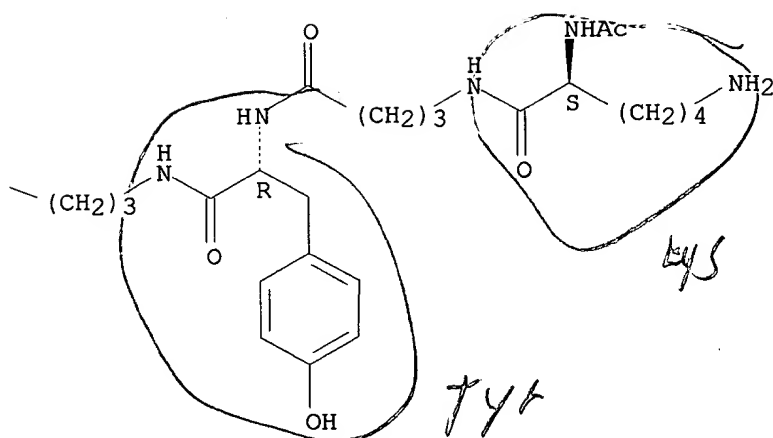
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N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.

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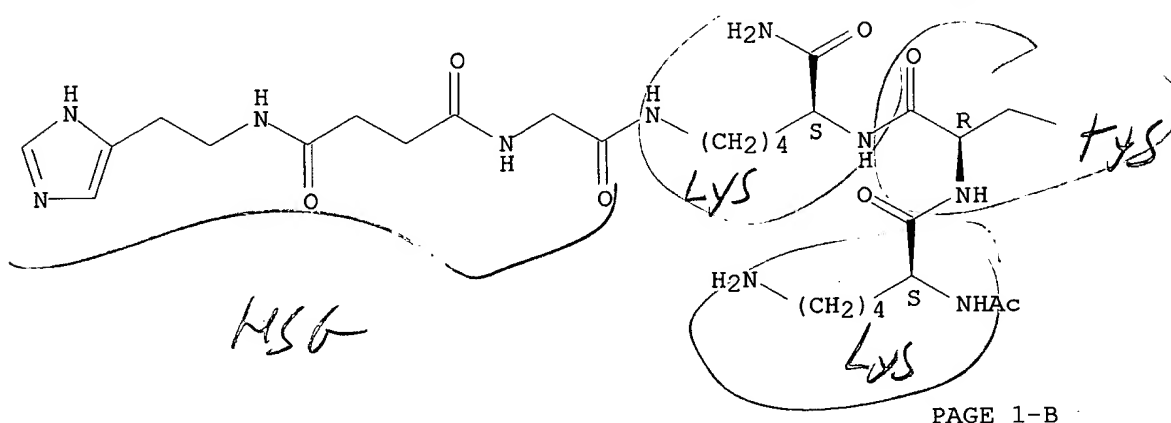


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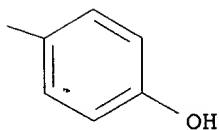
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Absolute stereochemistry.

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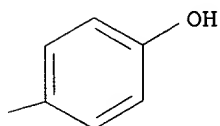
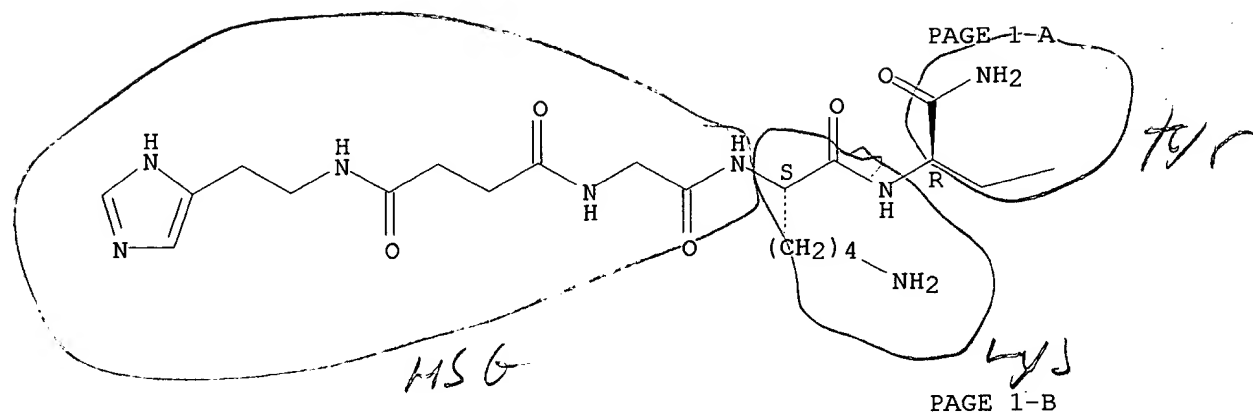
PAGE 1-B



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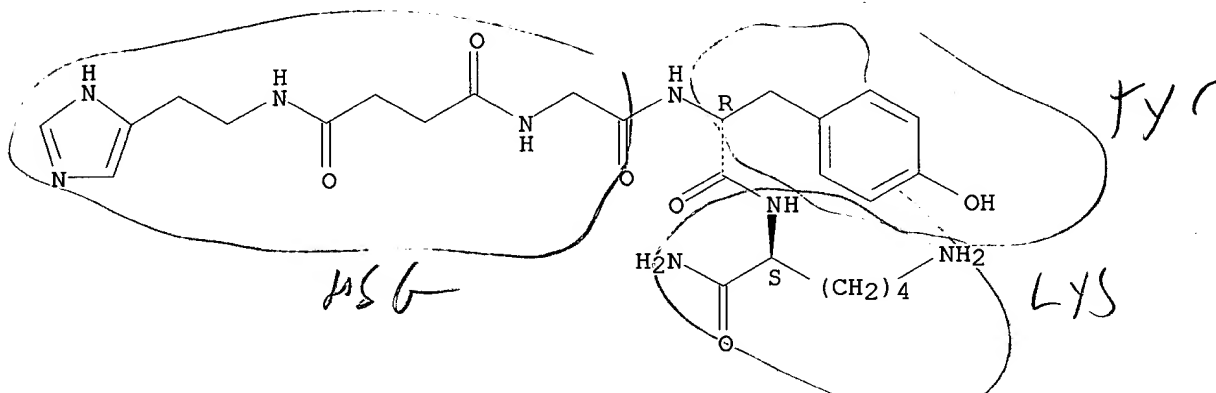
CN D-Tyrosinamide, N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl-L-lysyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 192370-49-3 HCAPLUS
 CN L-Lysinamide, N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl-D-tyrosyl- (9CI) (CA INDEX NAME)

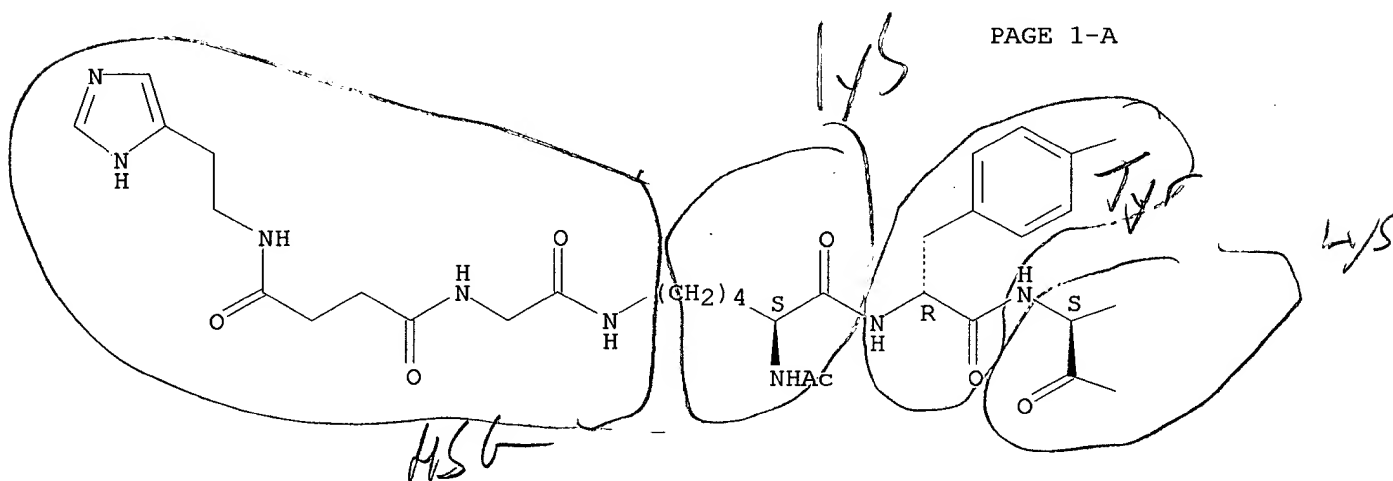
Absolute stereochemistry.



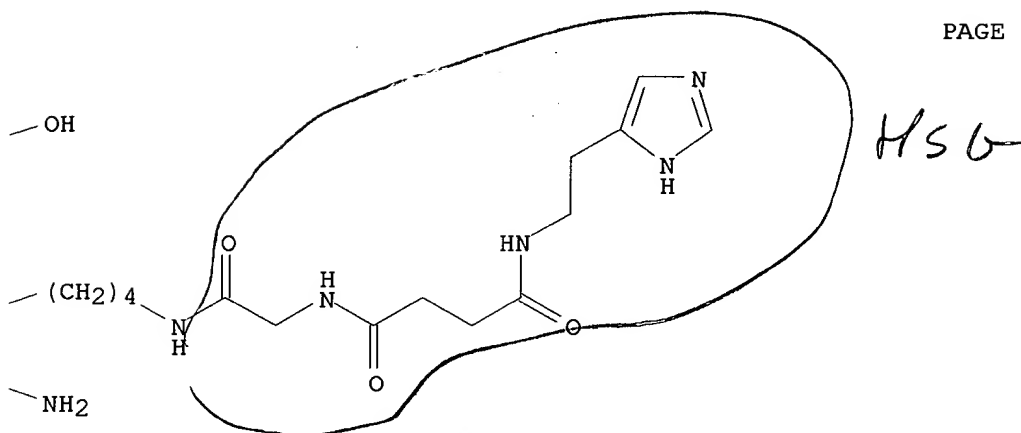
L21 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1995:979758 HCAPLUS
 DOCUMENT NUMBER: 124:111216
 TITLE: Intracellular uptake and catabolism of anti-IgM antibodies and bi-specific antibody-targeted hapten by B-lymphoma cells
 AUTHOR(S): Manetti, Corine; Doussal, Jean Marc Le; Rouvier, Eric; Gruaz-Guyon, Anne; Barbet, Jacques
 CORPORATE SOURCE: Imaging and Therapeutics Department, IMMUNOTECH, Marseille, 13276/9, Fr.
 SOURCE: International Journal of Cancer (1995), 63(2), 250-6
 CODEN: IJCNW; ISSN: 0020-7136
 PUBLISHER: Wiley-Liss
 DOCUMENT TYPE: Journal
 LANGUAGE: English

- AB The efficiency of radioimmunotherapy with iodine-labeled antibodies is often limited by intracellular internalization and catabolism after initial binding to the cellular targets. The authors have developed a technique called affinity enhancement system (AES) which uses bi-specific antibodies to target radiolabeled bivalent haptens to cells. This targeting method has been applied successfully to tumor imaging in colorectal cancer patients and is now considered for therapy. The authors have investigated the potential of this technique to target iodine radioisotopes by comparing it to targeting with covalently iodine-labeled antibodies in a rapidly internalizing antigenic system, the surface IgM of a B-lymphoma cell line. A 5-fold increase in the intracellular retention time of activity as compared to ^{125}I -labeled F(ab')_2 or IgG was obsd. The radiolabeled hapten did not undergo any catabolism after internalization. Resistance to cellular proteases and failure of recognition of the hapten by amino acid transporter systems may be potential explanations for these observations. This should make noncovalent targeting, particularly the AES, a method of choice to target modulating antigens for the therapy of malignant hemopathies.
- IT **173039-12-8D**, radiolabeled with indium-111 or iodine-125
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (intracellular uptake and catabolism of anti-IgM antibodies and bi-specific antibody-targeted hapten by B-lymphoma cells)
- RN 173039-12-8 HCAPLUS
- CN L-Lysinamide, N2-acetyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]-L-lysyl-D-tyrosyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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L21 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1994:701327 HCAPLUS

DOCUMENT NUMBER: 121:301327

TITLE: preparation of bihaptenic derivatives for binding for technetium or rhenium for diagnosis and therapy and immunological reactants comprising them

INVENTOR(S): Gruaz-Guyon, Anne; Le Doussal, Jean Marc; Delaage, Michel; Barbet, Jacques

PATENT ASSIGNEE(S): Immunotech Partners: Societe Anonyme Dite, Fr.

SOURCE: Eur. Pat. Appl., 13 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: French

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 595743	A1	19940504	EP 1993-430015	19931026
EP-595743	B1	20010314		

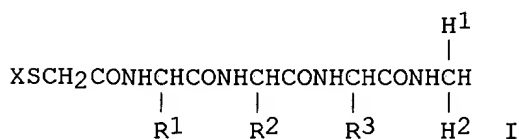
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE

FR 2697255	A1	19940429	FR 1992-13267	19921027
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CA 2109256	AA	19940428	CA 1993-2109256	19931026
AU 9350292	A1	19940512	AU 1993-50292	19931026
AU 669219	B2	19960530		
AT 199728	E	20010315	AT 1993-430015	19931026
ES 2155830	T3	20010601	ES 1993-430015	19931026
JP 06321809	A2	19941122	JP 1993-268835	19931027
			FR 1992-13267	A 19921027

PRIORITY APPLN. INFO.:

OTHER SOURCE(S): MARPAT 121:301327

GI



AB The title compds. [I; X = H, protecting group; R1, R2, R3 = amino acid side-chain; H1, H2 = hydrophilic hapten residue] are prepd. and used in diagnosis and therapy kits contg. I and an antibody (fragment) recognizing a particular cellular type/tissue and conjugated to a second antibody (fragment) recognizing a hapten group of I. N.alpha.-BOC-N.epsilon.-Fmoc-lysine bound to p-methylbenzylhydramine resin was coupled sequentially with N.alpha.-BOC-O-2,6-dichlorobenzyl-D-tyrosine, N.alpha.-BOC-N.epsilon.-Fmoc-lysine, N.alpha.-BOC-glycine, N.alpha.-BOC-glycine, and N.alpha.-BOC-glycine to give, after deprotection, treatment with succinic anhydride and histamine dihydrochloride, and cleavage from the resin, glycylglycylglycyl-N.epsilon.-(histamine-succinyl-glycine)-lysyl-D-tyrosyl-N.epsilon.-(histamine-succinyl-glycine)-lysylamide, which was reacted with S-acetylmercaptoacetic acid N-hydroxysuccinimide to give the title compd. II. This was reacted with ^{99m}Tc (Elumatic III, Cis biointernational) in a physiol. soln. (10 mCi/mL) in the presence of disodium tartrate to give ^{99m}Tc mercaptoacetyl-glycylglycylglycyl-N.epsilon.-(histamine-succinyl-glycine)-lysyl-D-tyrosyl-N.epsilon.-(histamine-succinyl-glycine)-lysylamide. An in vitro study on the linking of the ^{99m}Tc labeled probe on target cells were carried out.

IT **159173-61-2P**

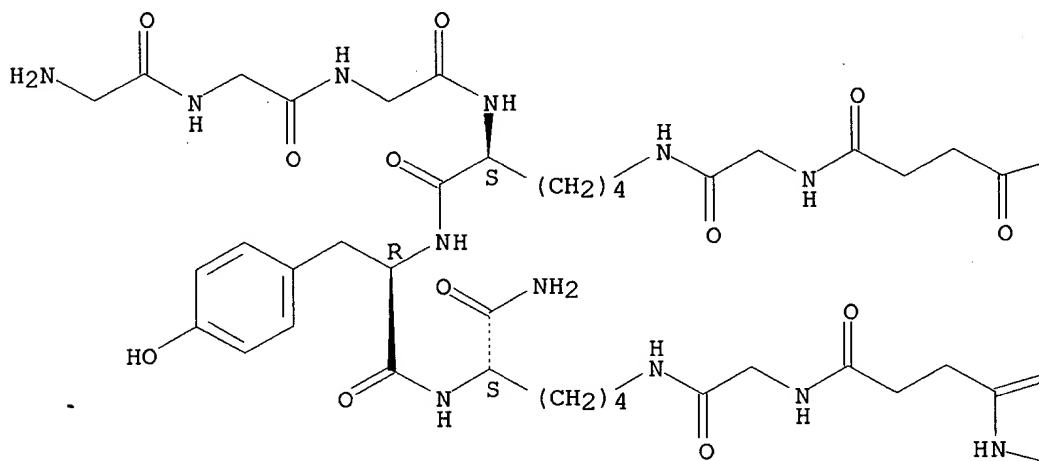
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as intermediate for bihaptenic derivs. for diagnosis and therapy kits)

RN 159173-61-2 HCAPLUS

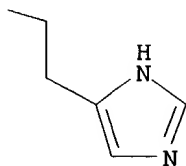
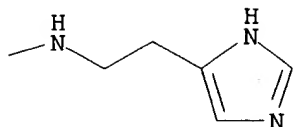
CN L-Lysinamide, glycylglycylglycyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]-L-lysyl-D-tyrosyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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IT 159173-58-7P 159173-59-8P

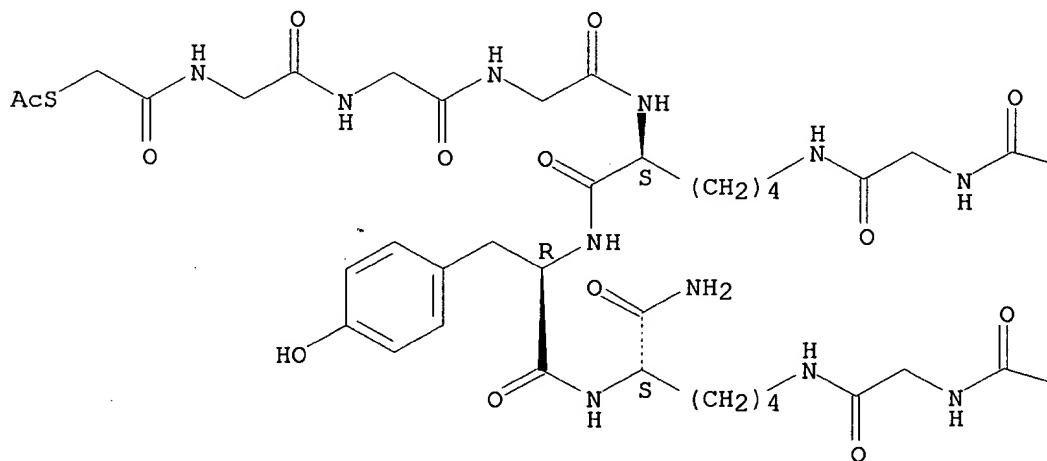
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(prepn. of, for diagnosis and therapy kits)

RN 159173-58-7 HCAPLUS

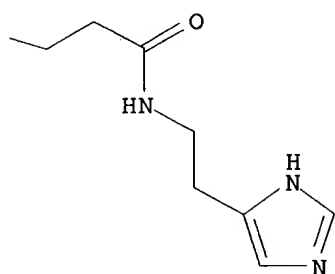
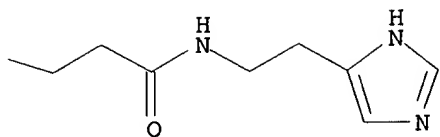
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Absolute stereochemistry.

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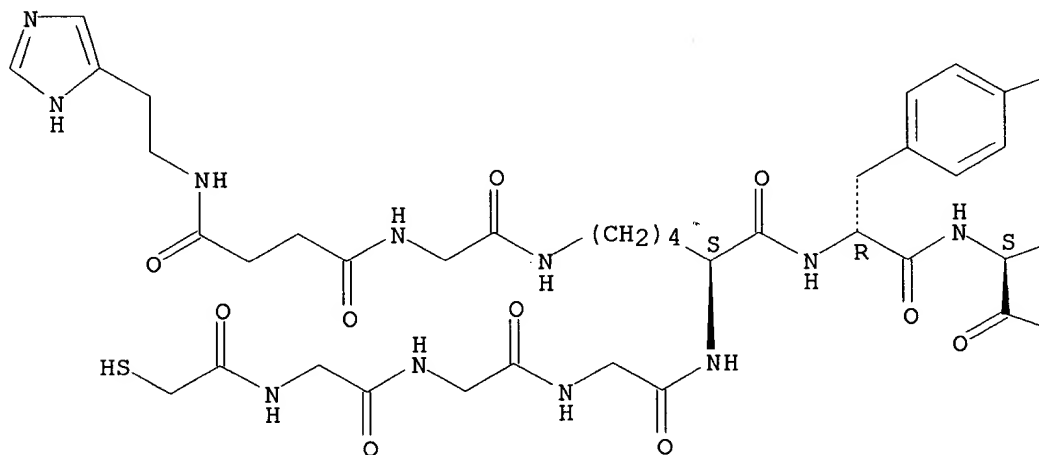


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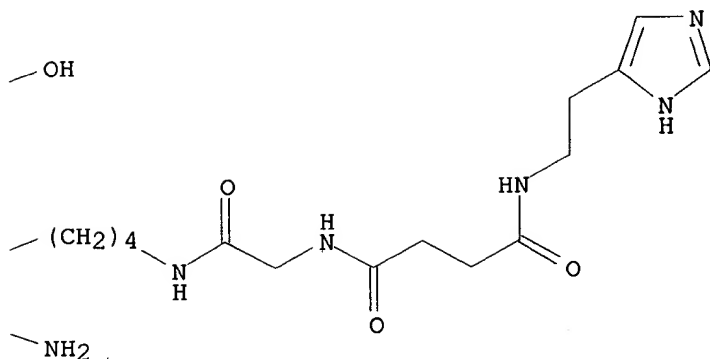
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Absolute stereochemistry.

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L21 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1992:17814 HCAPLUS

DOCUMENT NUMBER: 116:17814

TITLE: Radiolabeled hapten-derivatized peptides for tumor imaging with bispecific antibody conjugates

AUTHOR(S): Gruaz-Guyon, A.; Gras-Masse, H.; Le Doussal, J. M.

CORPORATE SOURCE: CHU St. Antoine, Paris, 75012, Fr.

SOURCE: Pept. 1990, Proc. Eur. Pept. Symp., 21st (1991), Meeting Date 1990, 822-5. Editor(s): Giralt, Ernest; Andreu, David. ESCOM Sci. Publ.: Leiden, Neth. CODEN: 57HNAI

DOCUMENT TYPE: Conference

LANGUAGE: English

AB Tumor imaging with ¹¹¹In- or ¹²⁵I-labeled monoclonal antibody F(ab')₂ fragments derivatized with bivalent haptens of histamine and DTPA was examd. in nude mice grafted with A375 human melanoma cells. Tumor targeting with F(ab')₂-F(ab') conjugates was better than that with F(ab')₂-F(ab') and tumor labeling with DTPA haptens was better than with dihistamine labeling.

IT **136687-41-7D**, radiolabeled monoclonal antibody F(ab')₂ fragment conjugates **138168-53-3D**, radiolabeled monoclonal antibody F(ab')₂ fragment conjugates

RL: BIOL (Biological study)

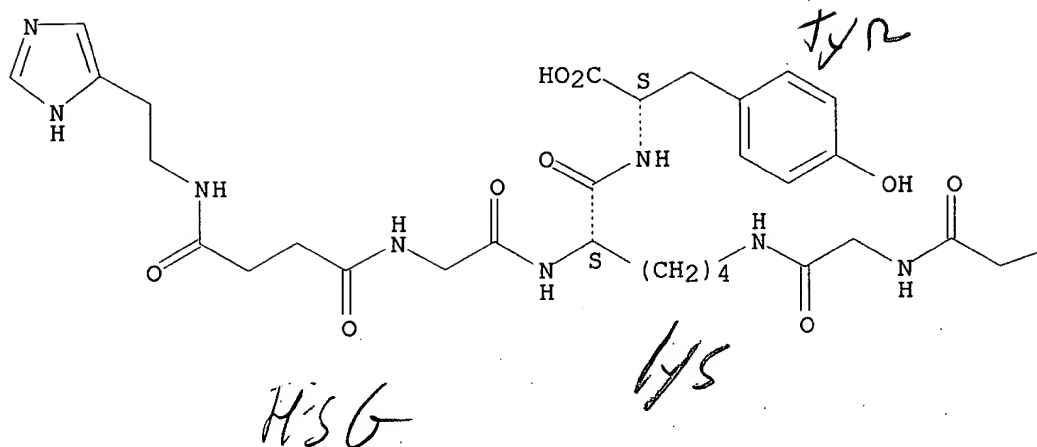
(imaging with, of tumor)

RN 136687-41-7 HCAPLUS

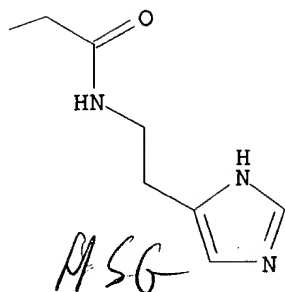
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Absolute stereochemistry.

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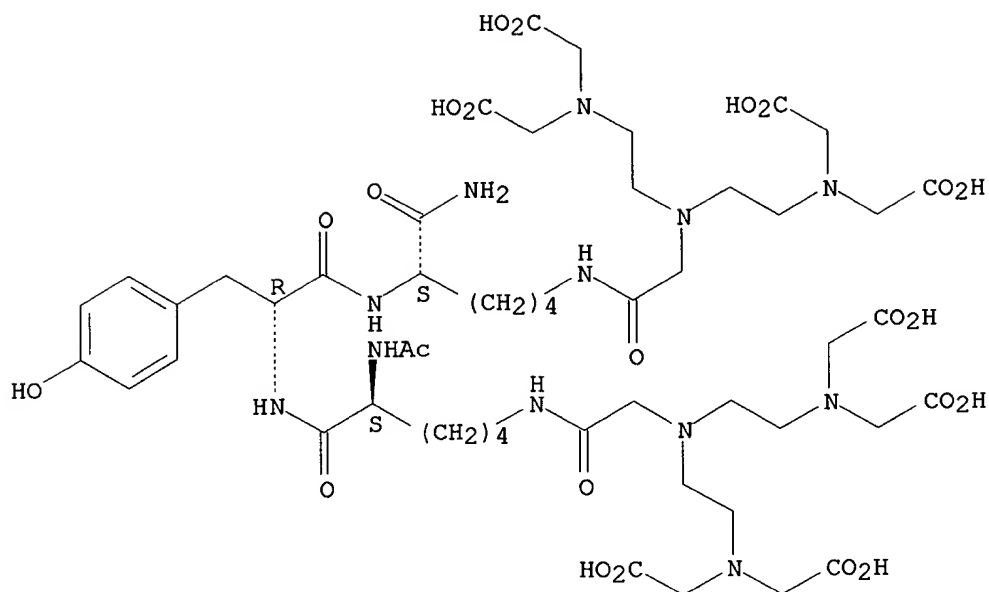
PAGE 1-B



RN 138168-53-3 HCAPLUS

CN L-Lysinamide, N2-acetyl-N6-[N,N-bis[2-[bis(carboxymethyl)amino]ethyl]glycyl]-L-lysyl-D-tyrosyl-N6-[N,N-bis[2-[bis(carboxymethyl)amino]ethyl]glycyl]-
(9CI) (CA INDEX NAME)

Absolute stereochemistry.



*This is same as
ited
US 823,746*

L21 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1991:578300 HCAPLUS
 DOCUMENT NUMBER: 115:178300
 TITLE: Hydrophilic derivatives containing effector group and
 2 haptens, their immunodiagnostic and
 immunotherapeutic use, and kits and immunological
 reagents containing them
 INVENTOR(S): Barbet, Jacques; Delaage, Michel; Gruaz-Guyon, Anne;
 Le Doussal, Jean Marc
 PATENT ASSIGNEE(S): Immunotech Partners, Fr.
 SOURCE: Eur. Pat. Appl., 8 pp.
 CODEN: EPXXDW
 DOCUMENT TYPE: Patent
 LANGUAGE: French
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 419387	A1	19910327	EP 1990-430018	19900920
EP 419387	B1	19961120		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
FR 2652004	A1	19910322	FR 1989-12622	19890921
FR 2652004	B1	19941028		
CA 2025607	AA	19910322	CA 1990-2025607	19900918
CA 2025607	C	20010807		
US 5274076	A	19931228	US 1990-584003	19900918
AU 9063034	A1	19910328	AU 1990-63034	19900920
AU 638488	B2	19930701		
JP 03173900	A2	19910729	JP 1990-248965	19900920
JP 2914737	B2	19990705		
AT 145338	E	19961215	AT 1990-430018	19900920
ES 2094750	T3	19970201	ES 1990-430018	19900920

PRIORITY APPLN. INFO.:

FR 1989-12622 A 19890921

AB Compds. are prepd. which contain 2 hydrophilic haptens and an effector group (an isotope or group that can be labeled with isotope, or an active principle or group to which an active principle can be attached), bonded by a nonpolymer connecting chain. The effector group is e.g. a scintigraphic radioisotope or a cytotoxic agent. The compds. are used in conjunction with (monoclonal) antibodies to specific cell types conjugated with (monoclonal) antibodies recognizing the hapten of the compd. and are useful for immunodiagnosis and immunotherapy. Thus, N.alpha.-DTPA-tyrosyl-N.epsilon.-DTPA-lysine, prepd. from tyrosyllysine and DTPA cyclic anhydride, was labeled with ^{111}In , and the resulting ^{111}In complex (I) was used in the immunoscintigraphic visualization of melanoma in nude mice. The mice, contg. human melanoma A375, were injected with a bispecific conjugate of a monoclonal anti-human melanoma F(ab')₂ fragment linked to a monoclonal anti-DTPA-Ir F(ab')₂ fragment. Later, I was injected and gamma camera images were obtained over time. The fixation obsd. was specific; the tumor did not accumulate significant amts. of radioactivity when the bispecific antibody conjugate was not injected or when the conjugate used had specificity for an antigen assocd. with another tumor. When ^{111}In -DTPA replaced I, the radioactivity was excreted rapidly and little specific fixation was obsd.

IT 136687-41-7P 136687-42-8P 136687-43-9P

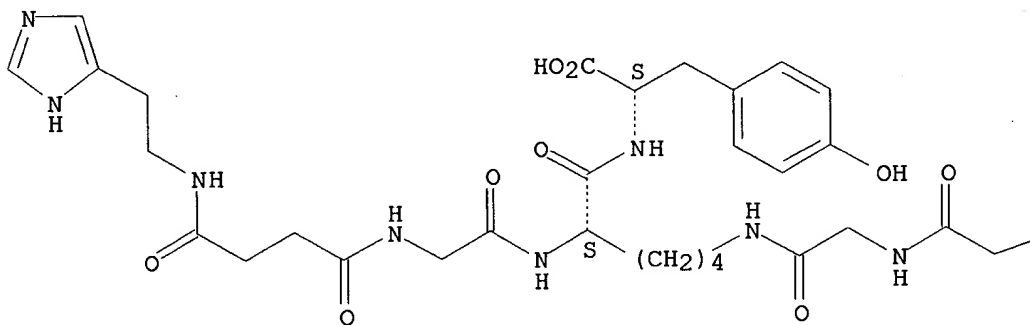
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, for immunodiagnosis and immunotherapy)

RN 136687-41-7 HCAPLUS

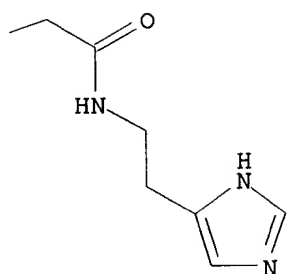
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Absolute stereochemistry.

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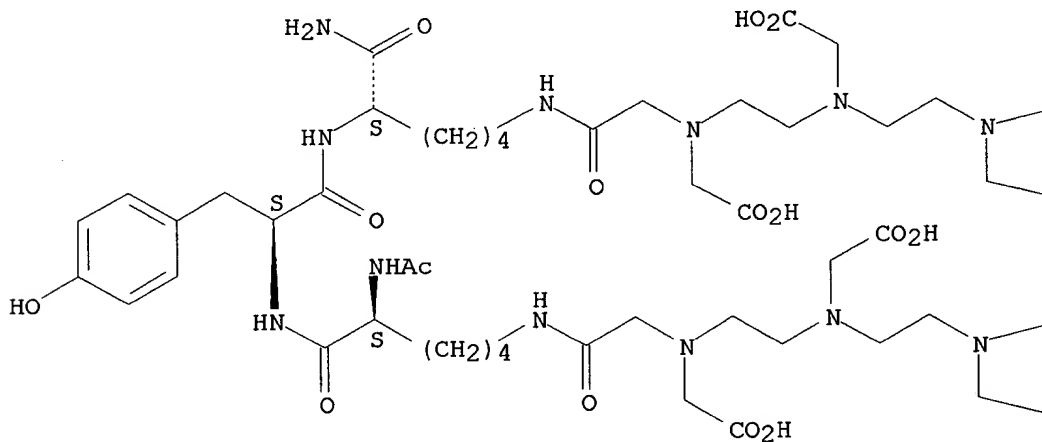


RN 136687-42-8 HCAPLUS

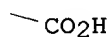
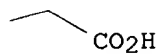
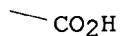
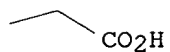
CN L-Lysinamide, N2-acetyl-N6-[N-[2-[[2-[bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]ethyl]-N-(carboxymethyl)glycyl]-L-lysyl-L-tyrosyl-N6-[N-[2-[[2-[bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]ethyl]-N-(carboxymethyl)glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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RN 136687-43-9 HCAPLUS

CN L-Lysinamide, N2-acetyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]-L-lysyl-L-tyrosyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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